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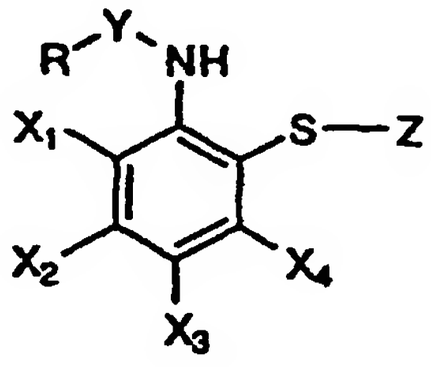
(54) CETP ACTIVITY INHIBITORS

(57) The present invention provides a CETP activity inhibitor comprising as an active ingredient a compound represented by the formula (I):



(I)

wherein R represents a straight chain or branched alkyl group; a straight chain or branched alkenyl group; a lower haloalkyl group; a substituted or unsubstituted cycloalkyl group; a substituted or unsubstituted cycloalkenyl group; a substituted or unsubstituted cycloalkylalkyl group; a substituted or unsubstituted aryl group, or a substituted or unsubstituted heterocyclic group, X_1, X_2, X_3, and X_4 may be the same or different and each represents a hydrogen atom, a

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halogen atom, a lower alkyl group, a lower haloalkyl group; a lower alkoxy group; a cyano group; a nitro group; an acyl group; or an aryl group, Y represents -CO- or -SO_2-, and Z represents a hydrogen atom or a mercapto-protecting group, or a prodrug compound, a pharmaceutically acceptable salt, or hydrate or solvate thereof. The compounds represented by the formula (I) can increase HDL and at the same time decrease LDL through selective inhibition of CETP activity and, therefore, is expected to be useful as a new type of a preventive or therapeutic agent for atherosclerosis or hyperlipidemia.

Description

TECHNICAL FIELD

[0001] This invention relates to a novel CETP activity inhibitor which comprises as an active ingredient a compound having a bis-(2-aminophenyl) disulfide structure or a 2-amino-phenylthio structure and more particularly to a pharmaceutical composition for treating or preventing atherosclerosis or hyperlipidemia. This invention also relates to a compound having a bis-(2-aminophehyl) disulfide structure or a 2-aminophenylthio structure, a prodrug compound, a pharmaceutically acceptable salt, hydrates or solvates of these compounds.

BACKGROUND ART

[0002] From the results of many epidemiological studies, it has been considered that there exists certain relation between atherosclerotic diseases and serum lipoprotein. For example, Badimon et al. (J. Clin. Invest. 85, 1234-1241 (1990)) reported that not only the prevention of development but also regression of atherosclerotic lesions were observed after intravenous injection of fractions containing HDL (high density lipoprotein) and VHDL (very high density lipoprotein) to cholesterol-loaded rabbits. Thus, regarding the relation between atherosclerotic diseases and serum lipoproteins, it is expected that HDL and VHDL may have antiatherosclerotic activity.

[0003] Recently, it has been elucidated that there are proteins that transfer lipids among serum lipoproteins, i.e., CETP (cholesterol ester transfer protein). The presence of CETP was first indicated by Nichols and Smith in 1965 (J. Lipid Res. 6, 206 (1965)). cDNA of the protein was later cloned by Drayna et al. in 1987. Molecular weight of the protein as glycoprotein is 74,000 Da. It is about 58,000 Da after complete removal of sugar chain. cDNA of this protein is composed of 1656 nucleotide residues and codes for 476 amino acids following signal peptide of 17 amino acid residues. Since around 44% of these amino acids are hydrophobic, the protein is highly hydrophobic and liable to be inactivated by oxidation. CETP is synthesized in organs like liver, spleen, adrenal, fat tissue, small intestine, kidney, skeletal muscle, and myocardium. It has been confirmed that CETP is synthesized in cells like macrophages derived from human monocytes, B lymphocytes, fat cells, small intestinal epithelial cells, $CaCo_2$ cells, and liver cells (for example, HepG2 cells derived from human hepatoma cells). In addition to these tissues, it is present in cerebrospinal fluid and seminal fluid, too. The presence is also confirmed in culture media of neuroblastoma and neuroglioma cells, and in chorioid plexus of sheep.

[0004] It has become apparent that CETP participates in metabolism of all the lipoproteins *in vivo* and plays important roles in reverse transfer system of cholesterol. It attracted attention as a system that prevents the accumulation of cholesterol into peripheral cells and functions as protective mechanism against atherosclerosis. In relation to HDL, which plays important roles in the reverse transfer system of cholesterol, a great number of epidemiological studies have shown that a decrease in CE (cholesterol esters) of HDL in blood represents one of the risk factors for coronary artery diseases. Activity of CETP differ depending on the species of animals and it has become apparent that cholesterol load does not bring about atherosclerosis in animals with low CETP activity, while it is easily produced in animals with high CETP activity. Absence of CETP results in high HDL-emia + low LDL (low density lipoprotein)-emia and brings about a state resistant to atherosclerosis. Thus, the importance of CETP as mediators of transfer of CE in HDL to blood LDL has become recognized in addition to the importance of HDL in blood.

[0005] Free cholesterol (FC) synthesized in the liver and secreted therefrom is taken up into very low density lipoprotein (VLDL). Next, VLDL is metabolized in the blood to LDL via intermediate density lipoprotein (IDL) by the action of lipoprotein lipase (LPL) and liver triglyceride lipase (HTGL). LDL is taken up to peripheral cells mediated by LDL receptor and, thus, FC is supplied to the cells.

[0006] Contrary to this flow from the liver to peripheral cells, there exists another flow of cholesterol from peripheral cells to the liver called cholesterol reverse transfer system. FC accumulated in peripheral cells is extracted by HDL, esterified on HDL through the action of LCAT (Lecithin: cholesterol acyltransferase) to form CE, transferred to the hydrophobic core portion of HDL, and HDL becomes matured to globular HDL particles. CE in HDL is transferred to apoB-containing lipoproteins such as VLDL, IDL, and LDL by CETP present in the blood. In exchange, TG is transferred to HDL in mole ratio of 1:1. CE that is transferred to apoB-containing lipoprotein is taken up by the liver via LDL receptor on it and, thus, cholesterol is transferred indirectly to the liver. There is mechanisms, too, by which HDL becomes CE-rich, apoprotein E-containing HDL by taking up apoprotein E secreted by macrophages and the like, which is then taken up directly to the liver via LDL receptor or remnant receptor. In another, the liver cells do not take up HDL particles, but take up selectively only CE in HDL. In still another, HDL particles are taken up by the liver cells via so-called HDL receptor.

[0007] In a state, in which CETP activity is augmented, CE in HDL is decreased and CE in VLDL, IDL and LDL is increased due to augmentation of CE transfer from HDL. Increases in uptake of IDL and LDL to the liver result in down-regulation of LDL receptor and increases in LDL in the blood. In contrast, in a state of CETP deficiency, HDL removes

cholesterol from peripheral cells with the aid of LCAT, increases its size gradually and acquires apoE. HDL that becomes apoE-rich is taken up by the liver via LDL receptor of the liver and catabolized. However, as the operation of this mechanism is not adequate in the human, retention of large HDL in the blood occurs and, as a result, cholesterol pool in the liver becomes smaller. LDL receptor becomes up-regulated and LDL is decreased.

[0008] Hence, by selectively inhibiting CETP, it is possible to decrease IDL, VLDL, and LDL that accelerate atherosclerosis and increase HDL that exhibits inhibitory action. Thus, it is anticipated that hitherto non-existent drugs useful for prevention or therapy of atherosclerosis or hyperlipidemia may be provided.

[0009] Very recently there have been reports on chemical compounds that aim at inhibition of such CETP activity.

[0010] For example, in Biochemical and Biophysical Research Communications 223, 42-47 (1996), dithiodipyridine derivatives and substituted dithiobenzene derivatives are disclosed as compounds capable of inactivating CETP through modification of cysteine residues. However, the literature neither discloses nor suggests the compounds such as those of the present invention which have a bis-(2-aminophenyl) disulfide structure or a 2-aminophenylthio structure.

[0011] WO95/06626 discloses Wiedendiol-A and Wiedendiol-B as CETP activity inhibitors, but there is no description suggesting the compounds of the present invention.

[0012] Furthermore, in JP-B-Sho 45-11132, JP-B-Sho 45-2892, JP-B-Sho 45-2891, JP-B-Sho 45-2731, and JP-B-Sho 45-2730, mercaptoanilides substituted with higher fatty acids such as o-isostearoylamino thiophenol are disclosed. However, in these publications, the atherosclerosis-preventing action is only referred to and there is no description of test examples that substantiate the action. There is also no description of CETP inhibitory activity. Nor is there description suggestive of compounds of the present invention.

[0013] There are several reports on the compounds having a bis-(2-aminophenyl) disulfide structure or a 2-aminophenylthio structure similar to those of the present application of invention.

[0014] For example, WO96/09406 discloses disulfide compounds such as 2-acetylaminophenyl disulfide and the like. However, the compounds of the publication are the ones that are useful for retrovirus, i.e., HIV-1, and usefulness as regards inhibitors of CETP activity has not been disclosed. There also is no description suggestive of the usefulness.

[0015] In JP-A-Hei 8-253454, diphenyl disulfide compounds such as 2,2'-di(pyrimidylamino)diphenyldisulfide and the like are disclosed. However, the compounds in this publication are the ones that have inhibitory action on production of IL-1β and on release of TNFα and there are no disclosure as regards the usefulness as inhibitors of CETP activity. There is even no description suggestive of the usefulness.

[0016] In JP-A-Hei 2-155937, bis-(acylaminophenyl) disulfide compounds such as 2,2'-diacetylaminodiphenyl disulfide and the like are disclosed. However, the compounds in this publication relates to the method of making vulcanized rubber filled with carbon black and there are no disclosure as regards the usefulness as inhibitors of CETP activity. There is also no description suggestive of the usefulness. In the claims recited in the publication, C_5-C_{12} cycloalkyl and cycloalkenyl are defined as R^9 and R^{10}, and as specific examples cyclohexyl and cyclohexenyl are described. However, in the publication no example that substantiates the use of the compound is shown and there is no description of the general method of production of the compounds.

[0017] JP-A-Hei 2-501772 discloses acylamino phenyl disulfide derivatives such as o-pivaloylaminophenyl disulfide and the like as intermediates for production of pyrazolone photocoupler. However, the invention described in this publication relates to the photo-element and not suggestive of the present invention. This publication also describes 2-cyclohexane carbonylamino phenylthio group as an example of coupling-off group of the coupler, but there is no description of examples that substantiate the use of the compound.

[0018] JP-A-Hei 8-171167 discloses thiophenol derivatives or disulfide derivatives such as 2-acetylamino thiophenol. However, the invention described in this publication relates to the silver halide emulsion and not suggestive of the present invention.

[0019] In JP-A-Hei 4-233908, disulfide derivatives such as bis-(2-acetoamidephenyl) disulfide and the like are disclosed. However, the compounds of this publication is disclosed as chain transfer agents and, thus, the publication does not suggest the present invention. As specific examples of R_3 in X,Y, a cyclohexyl group is disclosed, but the example substantiating the use and the general method of production are not described.

[0020] JP-A-Sho 63-157150 discloses amidophenyl disulfide derivatives such as o-pivalamidophenyl disulfide and the like as stabilizers. However, the invention of this publication relates to photo-element and is not suggestive of the present invention. In the claim recited in this publication, a cycloalkyl group is defined as R in the substituents V or Y of the stabilizer compounds, but the example substantiating the use and the general method of production are not described.

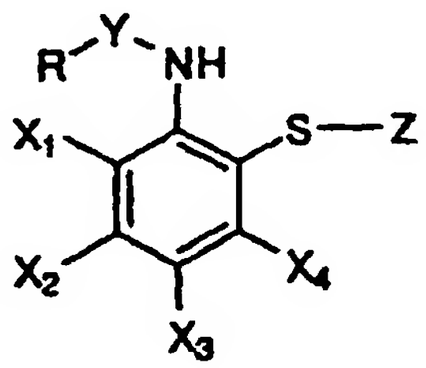
[0021] Bis-(amidophenyl) disulfide derivatives are also disclosed in JP-A-Hei 8-59900, JP-A-Hei 7-258472, JP-A-Hei 7-224028, JP-A-Hei 7-49554, JP-A-Hei 6-19037, JP-A-Hei 6-19024, JP-A-Hei 3-226750, JP-A-Hei 2-284146, JP-A-Hei 2-23338, JP-A-Hei 1-321432, JP-A-Hei 1-278543, and JP-B-Sho 47-357786. However, none of them discloses usefulness as inhibitors of CETP activity and there is no description suggestive of the usefulness.

DISCLOSURE OF THE INVENTION

[0022] As described above, the present inventors studied ardently in order to provide the compounds that selectively inhibit CETP activity and, as a result, found compounds useful as novel preventive or therapeutic agents of atherosclerosis or hyperlipidemia with new action mechanism which could increase HDL and at the same time decrease LDL, thereby completing the present invention.

[0023] The present invention relates to the compounds and medicaments as shown in the following (1) to (19) which have CETP activity inhibitory effect.

(1) A CETP activity inhibitor comprising as an active ingredient a compound represented by the formula (I):



(I)

wherein

R represents

a straight chain or branched C_{1-10} alkyl group;
a straight chain or branched C_{2-10} alkenyl group;
a halo-C_{1-4} lower alkyl group;
a substituted or unsubstituted C_{3-10} cycloalkyl group;
a substituted or unsubstituted C_{5-8} cycloalkenyl group;
a substituted or unsubstituted C_{3-10} cycloalkyl C_{1-10} alkyl group;
a substituted or unsubstituted aryl group;
a substituted or unsubstituted aralkyl group; or
a substituted or unsubstituted 5- or 6-membered heterocyclic group having 1-3 nitrogen, oxygen or sulfur atoms,

X_1, X_2, X_3, and X_4 may be the same or different and represents

a hydrogen atom;
a halogen atom;
a C_{1-4} lower alkyl group;
a halo-C_{1-4} lower alkyl group;
a C_{1-4} lower alkoxy group;
a cyano group;
a nitro group;
an acyl group; or
an aryl group,

Y represents

-CO-; or
-SO_2, and

Z represents

a hydrogen atom; or
a mercapto-protecting group,

a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

(2) A CETP activity inhibitor comprising as an active ingredient the compound described in the above (1), wherein

R represents

a straight chain or branched C_{1-10} alkyl group;
a straight chain or branched C_{2-10} alkenyl group;
a halo-C_{1-4} lower alkyl group substituted with 1-3 halogen atoms selected from fluorine, chlorine, and bromine;
a C_{3-10} cycloalkyl group, a C_{5-8} cycloalkenyl group, or a C_{3-10} cycloalkyl C_{1-10} alkyl group, each of which may have 1-4 substituents selected from the group consisting of

a straight chain or branched C_{1-10} alkyl group,
a straight chain or branched C_{2-10} alkenyl group,
a C_{3-10} cycloalkyl group,
a C_{5-8} cycloalkenyl group,
a C_{3-10} cycloalkyl C_{1-10} alkyl group,
an aryl group selected from phenyl, biphenyl, and naphthyl,
an oxo group, and
an aralkyl group having an aryl group selected from phenyl, biphenyl, and naphthyl; or

an aryl, aralkyl, or 5- or 6-membered heterocyclic group with 1-3 nitrogen, oxygen or sulfur atoms, each of which may have 1-4 substituents selected from the group consisting of

a straight chain or branched C_{1-10} alkyl group,
a straight chain or branched C_{2-10} alkenyl group,
a halogen atom selected from fluorine, chlorine, and bromine,
a nitro group, and
a halo-C_{1-4} lower alkyl group having a halogen atom selected from fluorine, chlorine, and bromine;

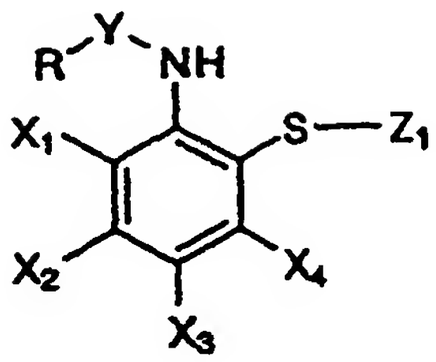
Z represents

a hydrogen atom;
a mercapto-protecting group selected from the group consisting of

a C_{1-4} lower alkoxymethyl group,
a C_{1-4} lower alkylthiomethyl group,
an aralkyloxymethyl group having an aryl group selected from phenyl, biphenyl, and naphthyl,
an aralkylthiomethyl group having an aryl group selected from phenyl, biphenyl, and naphthyl,
a C_{3-10} cycloalkyloxymethyl group,
a C_{5-8} cycloalkenyloxymethyl group,
a C_{3-10} cycloalkyl C_{1-10} alkoxymethyl group,
an aryloxymethyl group having an aryl group selected from phenyl, biphenyl, and naphthyl,
an arylthiomethyl group having an aryl group selected from phenyl, biphenyl, and naphthyl,
an acyl group,
an acyloxy group,
an aminocarbonyloxymethyl group,
a thiocarbonyl group, and
a thio group,

a prodrug compound thereof, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

(3) A CETP activity inhibitor comprising as an active ingredient the compound as described in the above (2), which is represented by the formula (I-1):



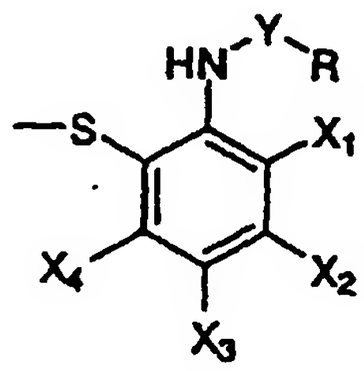
(I-1)

wherein R, X_1, X_2, X_3, X_4 and Y are the same as in the above (2) and

Z_1 represents

a hydrogen atom;

a group represented by the formula



wherein R, X_1, X_2, X_3, X_4, and Y are the same as described above;

$$-Y_1R_1,$$

wherein Y_1 represents -CO-; or
-CS-, and

R_1 represents

a substituted or unsubstituted straight chain or branched C_{1-10} alkyl group;
a C_{1-4} lower alkoxy group;
a C_{1-4} lower alkylthio group;
a substituted or unsubstituted amino group;
a substituted or unsubstituted ureido group;
a substituted or unsubstituted C_{3-10} cycloalkyl group;
a substituted or unsubstituted C_{3-10} cycloalkyl C_{1-10} alkyl group;
a substituted or unsubstituted aryl group;
a substituted or unsubstituted aralkyl group;
a substituted or unsubstituted arylalkenyl group;
a substituted or unsubstituted arylthio group;
a substituted or unsubstituted 5- or 6-membered heterocyclic group having 1-3 nitrogen, oxygen, or sulfur atoms; or
a substituted or unsubstituted 5- or 6-membered heteroarylalkyl group; or

$$-S-R_2,$$

wherein R_2 represents
a substituted or unsubstituted C_{1-4} lower alkyl group; or

a substituted or unsubstituted aryl group,
a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

(4) A CETP activity inhibitor comprising as an active ingredient the compound as described in the above (3), wherein

R_1 represents

a straight chain or branched C_{1-10} alkyl group which may have 1-3 substituents selected from the group consisting of

a halogen atom selected from fluorine, chlorine, and bromine,
a C_{1-4} lower alkoxy group,
an amino group that may be substituted with a C_{1-4} lower alkyl, acyl, or hydroxyl group,
a C_{1-4} lower alkylthio group,
a carbamoyl group,
a hydroxyl group,
an acyl group,
an acyloxy group having an acyl group,
a carboxyl group, and
an aryloxy group that may be substituted with a halogen atom selected from fluorine, chlorine, and bromine;

a C_{1-4} lower alkoxy group;
a C_{1-4} lower alkylthio group;
an amino or ureido group that may have 1-2 substituents selected from the group consisting of

a C_{1-4} lower alkyl group,
a hydroxyl group,
an acyl group, and
an aryl group that may be substituted with a lower C_{1-4} alkoxy group;

a C_{3-10} cycloalkyl or C_{3-10} cycloalkyl C_{1-10} alkyl group that may have substituents selected from the group consisting of

a straight or branched C_{1-10} alkyl group,
a C_{3-10} cycloalkyl group,
a C_{5-8} cycloalkenyl group,
an aryl group,
an amino group,
a C_{1-4} lower alkylamino group having a C_{1-4} lower alkyl group, and
an acylamino group having an acyl group;

an aryl group, an aralkyl group, an arylalkenyl group, or an arylthio group, each of which may have 1-4 substituents selected from the group consisting of

a C_{1-10} alkyl group,
a halogen atom selected from fluorine, chlorine, and bromine,
a nitro group,
a hydroxyl group,
a C_{1-4} lower alkoxy group,
a C_{1-4} lower alkylthio group,
an acyl group,
a halo-C_{1-4} lower alkyl group having a halogen atom selected from fluorine, chlorine, and bromine, and
an amino group that may be substituted with a C_{1-4} lower alkyl or acyl group;

a 5- or 6-membered heterocyclic group having 1-3 nitrogen, oxygen or sulfur atoms or a 5- or 6-membered

heteroarylalkyl group that may have 1-4 substituents selected from the group consisting of

a straight chain or branched C_{1-10} alkyl group,
a halogen atom selected from fluorine, chlorine, and bromine,
an acyl group,
an oxo group, and
an halo-C_{1-4} lower alkyl group having a halogen atom selected from fluorine, chlorine, and bromine; and

R_2 represents

a C_{1-4} lower alkyl group that may have 1-3 substituents selected from the group consisting of

a C_{1-4} lower alkoxy groups,
an amino group that may be substituted with a C_{1-4} lower alkyl or acyl group,
a C_{1-4} lower alkylthio group,
a carbamoyl group,
a hydroxyl group,
a carboxyl group,
an acyl group, and
a 5- or 6-membered heterocyclic group having 1-3 nitrogen, oxygen, or sulfur atoms; or

an aryl group that may have 1-4 substituents selected from the group consisting of

a C_{1-4} lower alkyl group,
a halogen atom selected from fluorine, chlorine, and bromine,
a nitro group,
a hydroxyl group,
a C_{1-4} lower alkoxy group,
a C_{1-4} lower alkylthio group,
an acyl group,
an amino group that may be substituted with a C_{1-4} lower alkyl or acyl group, and
a halo-C_{1-4} lower alkyl group having a halogen atom selected from fluorine, chlorine, and bromine,

a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

(5) A CETP activity inhibitor comprising as an active ingredient the compound as described in the above (1), which is selected from the group consisting of

bis-[2-(pivaloylamino)phenyl] disulfide;
bis-[2-(2-propylpentanoylamino)phenyl] disulfide;
bis-[2-(1-methylcyclohexanecarbonylamino)phenyl] disulfide;
bis-[2-(1-isopentylcyclopentanecarbonylamino)phenyl] disulfide;
bis-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] disulfide;
N-(2-mercaptophenyl)-2,2-dimethylpropionamide;
N-(2-mercaptophenyl)-1-isopentylcyclohexanecarboxamide;
N-(2-mercaptophenyl)-1-methylcyclohexanecarboxamide;
N-(2-mercaptophenyl)-1-isopentylcyclopentanecarboxamide;
N-(2-mercaptophenyl)-1-isopropylcyclohexanecarboxamide;
N-(4,5-dichloro-2-mercaptophenyl)-1-isopentylcyclohexanecarboxamide;
N-(4,5-dichloro-2-mercaptophenyl)-1-isopentylcyclopentanecarboxamide;
N-(2-mercapto-5-methylphenyl)-1-isopentylcyclohexanecarboxamide;
N-(2-mercapto-4-methylphenyl)-1-isopentylcyclohexanecarboxamide;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl]thioacetate;
S-[2-(1-methylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[2-(pivaloylamino)phenyl]phenylthioacetate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl) 2,2-dimethylthiopropionate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2-acetylamino-3-phenylthiopropionate;

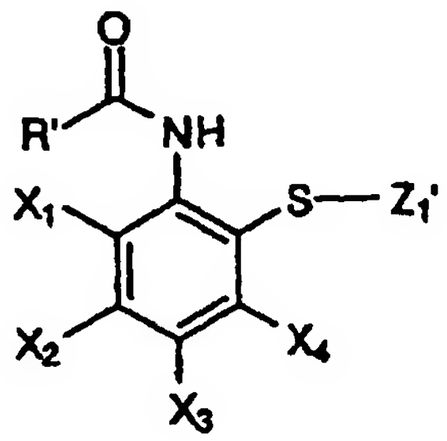
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] 3-pyridinethiocarboxylate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] chlorothioacetate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] methoxythioacetate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] thiopropionate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] phenoxythioacetate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2-methylthiopropionate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] 4-chlorophenoxythioacetate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] cyclopropanethiocarboxylate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2-acetylamino-4-carbamoylthiobutyrate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2-hydroxy-2-methylthiopropionate;
S-[2-(1-isopentylcyclopentanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[2-(1-isopentylcyclopentanecarbonylamino)phenyl] thioacetate;
S-[4,5-dichloro-2-(1-isopentylcyclohexanecarbonylamino)-phenyl] 2,2-dimethylthiopropionate;
S-[4,5-dichloro-2-(1-isopentylcyclopentanecarbonylamino)-phenyl] 2,2-dimethylthiopropionate;
S-[2-(1-isopentylcyclohexanecarbonylamino)-4-trifluoromethylphenyl] 2,2-dimethylthiopropionate;
O-methyl S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl monothiocarbonate;
S-[2-(1-methylcyclohexanecarbonylamino)phenyl] S-phenyl dithiocarbonate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] N-phenylthiocarbamate;
S-[2-(pivaloylamino)-4-trifluoromethylphenyl] 2,2-dimethylthiopropionate;
S-[4,5-dichloro-2-(1-cyclopropylcyclohexanecarbonylamino) phenyl] 2,2-dimethylthiopropionate;
S-[4,5-dichloro-2-(2-cyclohexylpropionylamino)phenyl] 2,2-dimethylthiopropionate;
S-[4,5-dichloro-2-(1-pentylcyclohexanecarbonylamino)-phenyl] 2,2-dimethylthiopropionate;
S-[4,5-dichloro-2-(1-cyclopropylmethylcyclohexane carbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[4,5-dichloro-2-(1-cyclohexylmethylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[4,5-dichloro-2-(1-isopropylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[4,5-dichloro-2-(1-isopentylcycloheptanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-(4,5-dichloro-2-(1-isopentylcyclobutanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[2-(1-isopentylcyclohexanecarbonylamino)-4-nitrophenyl] 2,2-dimethylthiopropionate;
S-[4-cyano-2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[4-chloro-2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[5-chloro-2-(1-isopentylcyclohexanecarbonylamino) phenyl] 2,2-dimethylthiopropionate;
S-[4-fluoro-2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[4,5-difluoro-2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2, 2-dimethylthiopropionate;
S-[5-fluoro-2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2,2-dimethyithiopropionate;
bis-[4,5-dichloro-2-(1-isopentylcyclohexanecarbonylamino)phenyl] disulfide;
2-tetrahydrofurylmethyl 2-(1-isopentylcyclohexanecarbonyl amino)phenyl disulfide;
N-(2-mercaptophenyl)-1-ethylcyclohexanecarboxamide;
N-(2-mercaptophenyl)-1-propylcyclohexanecarboxamide;
N-(2-mercaptophenyl)-1-butylcyclohexanecarboxamide;
N-(2-mercaptophenyl)-1-isobutylcyclohexanecarboxamide;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] cyclohexanethiocarboxylate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] thiobenzoate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] 5-carboxythiopentanoate;
S-[2-(1-isopentylcyclohexanecarbonylamino)-4-methylphenyl] thioacetate;
bis-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl] disulfide;
N-(2-mercaptophenyl)-1-(2-ethylbutyl)cyclohexanecarboxamide;
S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl] 2-methylthiopropionate;
S-[2-(1-isobutylcyclohexanecarbonylamino)phenyl] 2-methylthiopropionate;
S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl] 1-acetylpiperidine-4-thiocarboxylate;
S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl] thioacetate;
S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl] 2,2-dimethylthiopropionate;
S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl] methoxythioacetate;
S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino] phenyl] 2-hydroxy-2-methylthiopropionate;
S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl] 4-chlorophenoxythioacetate;
S-[2-(1-isobutylcyclohexanecarbonylamino)phenyl] 4-chlorophenoxythioacetate; and
S-(2-(1-isobutylcyclohexanecarbonylamino)phenyl] 1-acetylpiperidine-4-thiocarboxylate,

a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

(6) A prophylactic or therapeutic agent for hyperlipidemia comprising as an active ingredient the compound as described in the above in (1)-(5), a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

(7) A prophylactic or therapeutic agent for atherosclerosis comprising as an active ingredient the compound as described in the above in (1)-(5), a prodrug compound, a pharmaceutically acceptable salt, or hydrate or solvate thereof.

(8) A Compound represented by the formula (I-2):



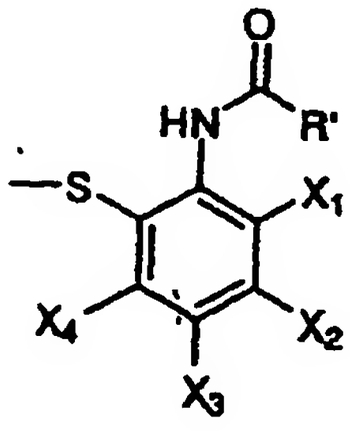
(I-2)

wherein R' represents

a substituted or unsubstituted C_{3-10} cycloalkyl group or
a substituted or unsubstituted C_{5-8} cycloalkenyl group;

X_1, X_2, X_3 and X_4 are as in the above (1); and Z_1' represents

a hydrogen atom;
a group represented by the formula:



wherein R', X_1, X_2, X_3, and X_4 are as described above;

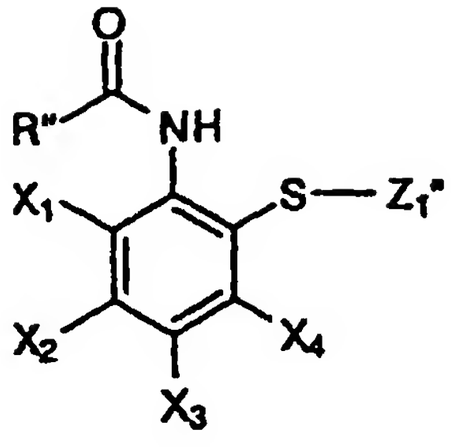
$$-Y_1R_1,$$

wherein Y_1 and R_1 are the same as in the above (3) or

$$-S-R_2,$$

wherein R_2 is the same as in the above (3),
a prodrug compound, a pharmaceutically acceptable salt, hydrate,or solvate thereof.

(9) A compound as described above in (8), which is represented by the formula (I-3):



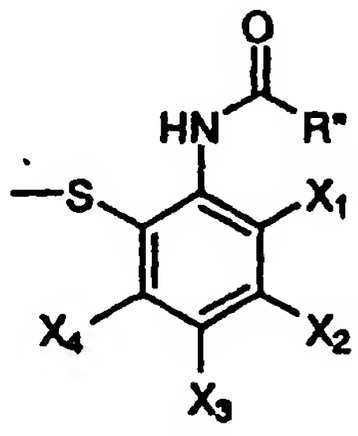
(I-3)

wherein R" represents

a 1-substituted-C_{3-10} cycloalkyl group or
a 1-substituted-C_{5-8} cycloalkenyl group;

X_1, X_2, X_3, and X_4 are the same as in the above (1); and Z_1" represents

a hydrogen atoms;
a group represented by the formula:



wherein R", X_1, X_2, X_3, and X_4 are as described above;

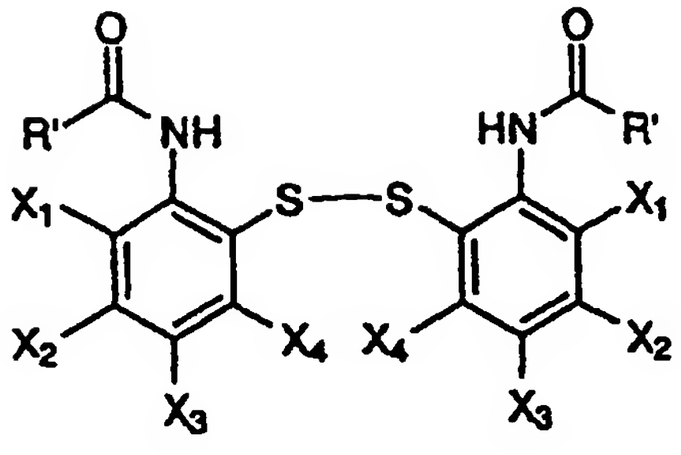
$$-Y_1R_1,$$

wherein Y_1 and R_1 are the same as in the above (3); or

$$-S-R_2,$$

wherein R_2 is the same as in the above (3),
a prodrug compound, a pharmaceutically acceptable salt, hydrate,or solvate thereof.

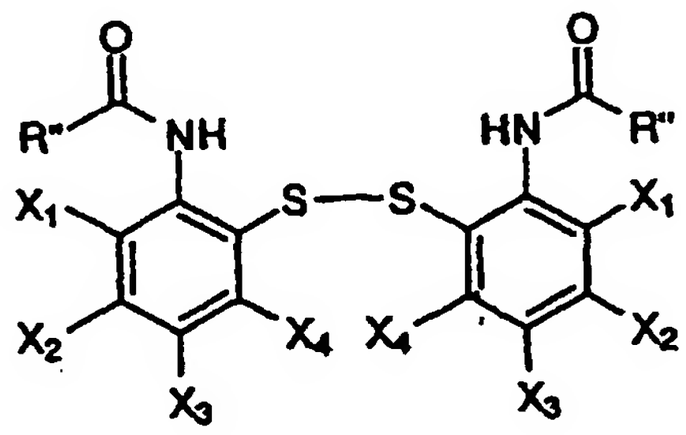
(10) A compound as described in the above (8), which is represented by the formula (II):



(II)

wherein R', X_1, X_2, X_3, and X_4 are the same as in the above (8),
a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

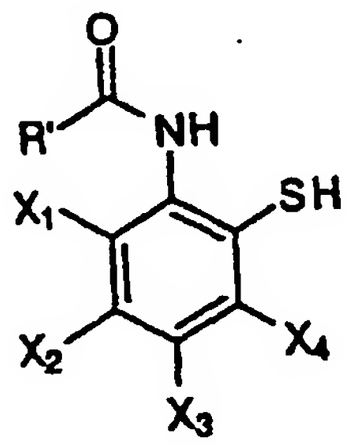
(11) A compound as described in the above (9), which is represented by formula (II-1):



(II-1)

wherein R", X_1, X_2, X_3, and X_4 are the same as in the above (9),
a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

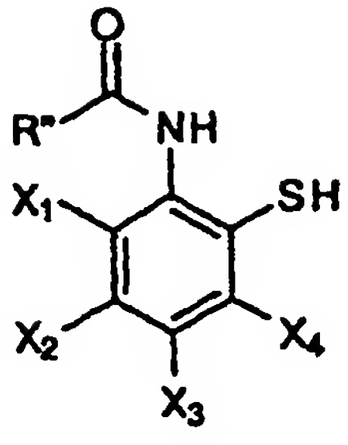
(12) A compound as described in the above (8), which represented by the formula (III):



(III)

wherein R', X_1, X_2, X_3, and X_4 are the same as in the above (8),
a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

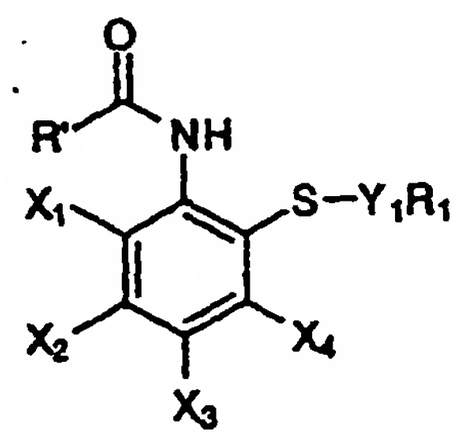
(13) A compound as described in the above (9), which is represented by formula (III-1):



(III-1)

wherein R", X_1, X_2, X_3, and X_4 are the same as in the above (9),
a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

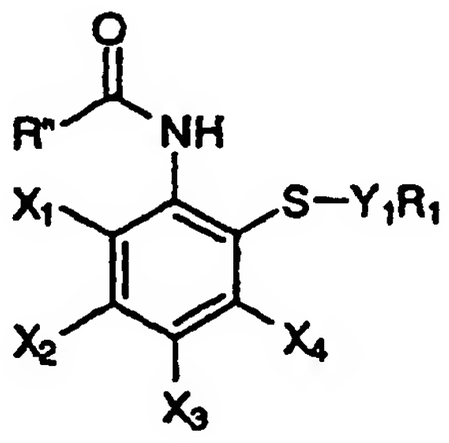
(14) A compound as described in the above (8), which is represented by formula (IV):



(IV)

wherein R', X_1, X_2, X_3, X_4, Y_1, and R_1 are the same as in the above (8),
a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

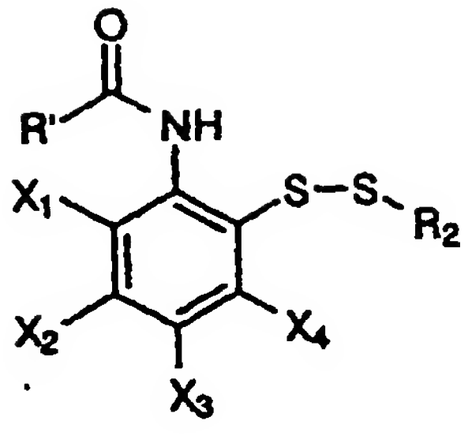
(15) A compound as described in the above (9), which is represented by formula (IV-1):



(IV-1)

wherein R", X_1, X_2, X_3, X_4, Y_1, and R_1 are the same as in the above (9),
a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

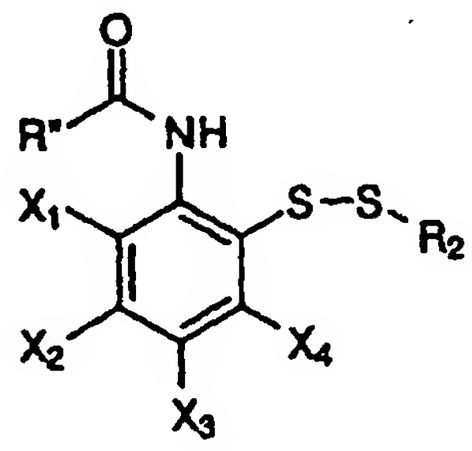
(16) A compound as described in the above (8), which is represented by formula (V):



(V)

wherein R', X_1, X_2, X_3, X_4, and R_2 are the same as in the above (8),
a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

(17) A compound as described in the above (9), which is represented by formula (V-1):



(V-1)

wherein R", X_1, X_2, X_3, X_4, and R_2 are the same as in the above (9),
a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

(18) A compound as described in the above (8), which is selected from the group consisting of

bis-[2-(1-methylcyclohexanecarbonylamino)phenyl] disulfide;
bis-[2-(1-isopentylcyclopentanecarbonylamino)phenyl] disulfide;
bis-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] disulfide;
N-(2-mercaptophenyl)-1-isopentylcyclohexanecarboxamide;
N-(2-mercaptophenyl)-1-methylcyclohexanecarboxamide;
N-(2-mercaptophenyl)-1-isopentylcyclopentanecarboxamide;
N-(2-mercaptophenyl)-1-isopropylcyclohexanecarboxamide;
N-(4,5-dichloro-2-mercaptophenyl)-1-isopentylcyclohexanecarboxamide;
N-(4,5-dichloro-2-mercaptophenyl)-1-isopentylcyclopentanecarboxamide;
N-(2-mercapto-5-methylphenyl)-1-isopentylcyclohexanecarboxamide;
N-(2-mercapto-4-methylphenyl)-1-isopentylcyclohexanecarboxamide;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] thioacetate;
S-[2-(1-methylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2-acetylamino-3-phenylthiopropionate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] 3-pyridinethiocarboxylate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] chlorothioacetate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] methoxythioacetate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] thiopropionate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] phenoxythioacetate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2-methylthiopropionate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] 4-chlorophenoxythioacetate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] cyclopropanethiocarboxylate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2-acetylamino-4-carbamoylthiobutyrate;

S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2-hydroxy-2-methylthiopropionate;
S-[2-(1-isopentylcyclopentanecarbonylamino)phenyl] 2,2-dimethylpropionate;
S-[2-(1-isopentylcyclopentanecarbonylamino)phenyl] thioacetate;
S-[4,5-dichloro-2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2, 2-dimethylthiopropionate;
S-[4,5-dichloro-2-(1-isopentylcyclopentanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[2-(1-isopentylcyclohexanecarbonylamino)-4-trifluoromethylphenyl] 2,2-dimethylthiopropionate;
O-methyl S-[2-(1-isopentylcyclohexanecarbonylamino) phenyl] monothiocarbonate;
S-[2-(1-methylcyclohexanecarbonylamino)phenyl] S-phenyl dithiocarbonate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] N-phenylthiocarbamate;
S-[4,5-dichloro-2-(1-cyclopropylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[4,5-dichloro-2-(1-pentylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[4,5-dichloro-2-(1-cyclopropylmethylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[4,5-dichloro-2-(1-cyclohexylmethylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropioate;
S-[4,5-dichloro-2-(1-isopropylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[4,5-dichloro-2-(1-isopentylcycloheptanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[4,5-dichloro-2-(1-isopentylcyclobutanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[2-(1-isopentylcyclohexanecarbonylamino)-4-nitrophenyl] 2,2-dimethylthiopropionate;
S-[4-cyano-2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[4-chloro-2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[5-chloro-2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[4-fluoro-2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[4,5-difluoro-2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[5-fluoro-2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
bis-[4,5-dichloro-2-(1-isopentylcyclohexanecarbonylamino)phenyl] disulfide;
2-tetrahydrofurylmethyl 2-(1-isopentylcyclohexanecarbonylamino)phenyl disulfide;
N-(2-mercaptophenyl)-1-ethylcyclohexanecarboxamide;
N-(2-mercaptophenyl)-1-propylcyclohexanecarboxamide;
N-(2-mercaptophenyl)-1-butylcyclohexanecarboxamide;
N-(2-mercaptophenyl)-1-isobutylcyclohexanecarboxamide;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] cyclohexanethiocarboxylate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] thiobenzoate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] 5-carboxythiopentanoate;
S-[2-(1-isopentylcyclohexanecarbonylamino)-4-methylphenyl] thioacetate;
bis-[2-(1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl]disulfide;
N-(2-mercaptophenyl)-1-(2-ethylbutyl) cyclohexanecarboxamide;
S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl] 2-methylthiopropionate;
S-[2-(1-isobutylcyclohexanecarbonylamino]phenyl] 2-methylthiopropionate;
S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl] 1-acetylpiperidine-4-thiocarboxylate;
S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl] thioacetate;
S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl] 2,2 -dimethylthiopropionate;
S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl] methoxythioacetate;
S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl] 2-hydroxy-2-methylpropionate;
S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl] 4-chlorophenoxythioacetate;
S-[2-(1-isobutylcyclohexanecarbonylamino)phenyl] 4-chlorophenoxythioacetate; and
S-[2-(1-isobutylcyclohexanecarbonylamino)phenyl] 1-acetylpiperidine-4-thiocarboxylate,

a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

(19) A phamaceutical composition comprising as an active ingredient the compound as described in the above (8)-(18), a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

(20) Use of the compound represented by the above formula (I), a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof, for production of a CETP activity inhibitor.

(21) Use of the compound represented by the above formula (I), a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof, for production of a prophylactic or therapeutic agent for hyperlipidemia.

(22) Use of the compound represented by the above formula (I), a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof, for production of a prophylactic or therapeutic agent for atherosclerosis.

(23) A method for inhibition of CETP activity comprising administering to patients the compound represented by the above formula (I), a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

(24) A method for prevention or therapy of hyperlipidemia comprising administering to patients the compound rep-

resented by the above formula (I), a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

(25) A method for prevention or therapy of atherosclerosis comprising administering to patients the compound represented by the above formula (I), a prodrug compound, a pharmaceutically acceptable salt, or hydrate, or solvate thereof.

[0024] The term "straight chain or branched C_{1-10} alkyl group" used herein means an alkyl group having 1-10 carbon atoms which may be straight or branched. Specific examples thereof include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, 1-ethylbutyl, 2-ethylbutyl, 1-propylbutyl, 1,1-dimethylbutyl, 1-isobutyl-3-methylbutyl, 1-ethylpentyl, 1-propylpentyl, 1-isobutylpentyl, 2-ethylpentyl, 2-isopropylpentyl, 2-tert-butylpentyl, 3-ethylpentyl, 3-isopropylpentyl, 4-methylpentyl, 1,4-dimethylpentyl, 2,4-dimethylpentyl, 1-ethyl-4-methylpentyl, hexyl, 1-ethylhexyl, 1-propylhexyl, 2-ethylhexyl, 2-isopropylhexyl, 2-tert-butylbexyl, 3-ethylhexyl, 3-isopropylhexyl, 3-tert-butylhexyl, 4-ethylhexyl, 5-methylhexyl, heptyl, 1-ethylheptyl, 1-isopropylheptyl, 2-ethylheptyl, 2-isopropylheptyl, 3-propylheptyl, 4-propylheptyl, 5-ethylheptyl, 6-methylheptyl, octyl, 1-ethyloctyl, 2-ethyloctyl, nonyl, 1-methylnonyl, 2-methylnonyl, decyl, and the like groups. A straight chain or branched alkyl group having 1-8 carbon atoms is preferred.

[0025] The term "C_{1-4} lower alkyl group" used herein means an alkyl group having 1-4 carbon atoms, and specifically includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, and the like groups.

[0026] The term "straight chain or branched C_{2-10} alkenyl group" means an alkenyl group having 2-10 carbon atoms with at least one or more double bonds, which may be straight or branched. Specific examples thereof include allyl, vinyl, isopropenyl, 1-propenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, 1-methyl-1-butenyl, crotyl, 1-methyl-3-butenyl, 3-methyl-2-butenyl, 1,3-dimethyl-2-butenyl, 1-pentenyl, 1-methyl-2-pentenyl, 1-ethyl-3-pentenyl, 4-pentenyl, 1,3-pentadienyl, 2,4-pentadienyl, 1-hexenyl, 1-methyl-2-hexenyl, 3-hexenyl, 4-hexenyl, 1-butyl-5-hexenyl, 1,3-hexadienyl, 2,4-hexadienyl, 1-heptenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl, 1,3-heptadienyl, 2,4-heptadienyl, 1-octenyl, 2-octenyl, 3-octenyl, 4-octenyl, 5-octenyl, 6-octenyl, 7-octenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 4-nonenyl, 5-nonenyl, 6-nonenyl, 7-nonenyl, 8-nonenyl, 9-decenyl, and the like groups. An alkenyl group having 2-8 carbon atoms, which may be straight or branched, is preferred.

[0027] The term "halogen atom" means fluorine, chlorine, and bromine atoms.

[0028] The term "halo-C_{1-4} alkyl group" means the above-described C_{1-4} lower alkyl group substituted with 1-3 halogens, which may be the same or different. Specific examples thereof include fluoromethyl, chloromethyl, bromomethyl, difluoromethyl, dichloromethyl, trifluoromethyl, trichloromethyl, chloroethyl, difluoroethyl, trifluoroethyl, pentachloroethyl, bromopropyl, dichloropropyl, trifluorobutyl, and the like groups. Trifluoromethyl and chloroethyl are preferred.

[0029] The term "C_{1-4} lower alkoxy group" means the alkoxy group containing the C_{1-4} lower alkyl group as described above. Examples thereof include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, and the like groups.

[0030] The term "C_{1-4} lower alkylthio group" means the alkylthio group containing the C_{1-4} lower alkyl group as described above. Examples thereof include methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, and the like groups.

[0031] The term "C_{3-10} cycloalkyl group" means a cycloalkyl group having 3-10 carbon atoms, which may be monocyclic or polycyclic. Examples thereof include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, octahydroindenyl, decahydronaphthyl, bicyclo[2.2.1]heptyl, adamantyl, and the like groups. Preferred are those having 5-7 carbon atoms, including cyclopentyl, cyclohexyl, and cycloheptyl.

[0032] The term "C_{5-8} cycloalkenyl group" means a cycloalkenyl group having 5-8 carbon atoms with one or more double bonds on the ring. Examples thereof include cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclopentadienyl, cyclohexadienyl, cycloheptadienyl, cyclooctadienyl, and the like groups. Preferred are those with 5-7 carbon atoms, including cyclopentenyl, cyclohexenyl, and cycloheptenyl.

[0033] The term "C_{3-10} cycloalkyl C_{1-10} alkyl group" means the above-described straight chain or branched C_{1-10} alkyl group substituted with the above-described C_{3-10} cycloalkyl group. Specific examples thereof include cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclohexyl cyclopentylmethyl, dicyclohexylmethyl, 1-cyclopentylethyl, 1-cyclohexylethyl, 2-cyclopropylethyl, 2-cyclopentylethyl, 2-cyclohexylethyl, 2-cycloheptylethyl, 1-cyclohexyl-1-methylethyl, 1-cyclohexylpropyl, 2-cyclopentylpropyl, 3-cyclobutylpropyl, 3-cyclopentylpropyl, 3-cyclohexylpropyl, 3-cycloheptylpropyl, 1-cyclopropyl-1-methylpropyl, 1-cyclohexyl-2-methylpropyl, 1-cyclopentylbutyl, 1-cyclohexylbutyl, 3-cyclohexylbutyl, 4-cyclopropylbutyl, 4-cyclobutylbutyl, 4-cyclopentylbutyl, 1-cyclohexyl-1-methylhutyl, 1-cyclopentyl-2-ethylbutyl, 1-cyclohexyl-3-methylbutyl, 1-cyclopentylpentyl, 1-cyclohexylpentyl, 1-cyclohexylmethylpentyl, 2-cyclohexylpentyl, 2-cyclohexylmethylpentyl, 3-cyclopentylpentyl, 1-cyclohexyl-4-methylpentyl, 5-cyclopentylpentyl, 1-cyclopentylbexyl, 1-cyclohexylbexyl, 1-cyclopentylmethylhexyl, 2-cyclopentylhexyl, 2-cyclopropylethylhexyl, 3-cyclopentylbexyl, 1-cyclohexylheptyl, 1-cyclopentyl-1-methylheptyl, 1-cyclohexyl-1,6-dimethylheptyl, 1-cycloheptyloctyl, 2-cyclopentyloctyl, 3-cyclohexyloctyl, 2-cyclopentylmethyloctyl, 1-cyclopentylnonyl, 1-cyclohexylnonyl, 3-cyclopropylnonyl, 1-cyclopentyl-

decyl, 1-cyclohexylundecyl, 1-cyclopentyltridecyl, 2-cyclohexyltridecyl, and the like groups.

[0034] The "aryl group" includes phenyl, naphthyl, anthryl, phenanthryl, biphenyl, and the like groups. Phenyl, naphthyl, and biphenyl groups are preferred.

[0035] The "aralkyl group" means the above-described C_{1-4} lower alkyl group substituted with one or more aryl groups as described above. Examples thereof include benzyl, benzhydryl, trityl, phenethyl, 3-phenylpropyl, 2-phenylpropyl, 4-phenylbutyl, naphthylmethyl, 2-naphthylethyl, 4-biphenylmethyl, 3-(4-biphenyl) propyl, and the like groups.

[0036] The "arylalkenyl group" means an alkenyl group having 2-4 carbon atoms substituted with the above-described aryl group. Examples thereof include 2-phenylvinyl, 3-phenyl-2-propenyl, 3-phenyl-2-methyl-2-propenyl, 4-phenyl-3-butenyl, 2-(1-naphthyl)vinyl, 2-(2-naphthyl)vinyl, 2-(4-biphenyl)vinyl, and the like groups.

[0037] The "arylthio group" means an arylthio group containing the above-described aryl group and specifically include phenylthio, naphthylthio, and the like groups.

[0038] The "heterocyclic ring group" means 5- and 6-membered aromatic or non-aromatic heterocyclic ring groups containing at least one or more, specifically 1-4, preferably 1-3, hetero atoms selected from nitrogen, oxygen, and sulfur atoms. Specific examples thereof include aromatic heterocyclic rings such as thiatriazolyl, tetrazolyl, dithiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, oxazolyl, pyrazolyl, pyrrolyl, furyl, thienyl, tetrazinyl, triazinyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyridyl, or the like groups and non-aromatic heterocyclic rings such as dioxoranyl, pyrrolidinyl, tetrahydrofuryl, tetrahydrothienyl, dithiadiazinyl, thiadiazinyl, morpholino, morpholinyl, oxazinyl, thiazinyl, piperazinyl, piperidyl, piperidino, pyranyl, thiopyranyl, or the like groups. Preferable groups are aromatic heterocyclic (heteroaryl) groups including furyl, thienyl, pyrrolyl, pyridyl, and the like and non-aromatic heterocyclic groups containing at least one nitrogen atom, including pyrrolidinyl, tetrahydrofuryl, piperazinyl, piperidyl, piperidino, and the like groups.

[0039] The "heteroarylalkyl group" means the above-described C_{1-4} lower alkyl group substituted with the above-described 5- or 6-membered aromatic heterocyclic (heteroaryl) group and specifically include 2-thienylmethyl, 2-furylmethyl, 2-pyridylmethyl, 3-pyridylmethyl, 2-thienyl-2-ethyl, 3-furyl-1-ethyl, 2-pyridyl-3-propyl, and the like groups.

[0040] The "acyl group" specifically includes formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, acryloyl, propioloyl, metacryloyl, crotonoyl, benzoyl, naphthoyl, toluoyl, hydroatropoyl, atropoyl, cinnamoyl, furoyl, thenoyl, nicotinoyl, isonicotinoyl, glucoloyl, lactoyl, glyceroyl, tropoyl, benzyloyl, salicyloyl, anisoyl, vaniloyl, veratoroyl, piperoniroyl, protocatechoyl, galloyl, cyclopentanecarbonyl, cyclohexanecarbonyl, cycloheptanecarbonyl, 1-methyl cyclohexanecarbonyl, 1-isopentylcyclopentanecarbonyl, 1-isopentyl cyclohexanecarbonyl, tert-butoxycarbonyl, methoxycarbonyl, ethoxycarbonyl, 2-(1-isopentylcyclohexanecarbonylamino)phenylthiocarbonyl, and the like groups. Preferred are acetyl, tertbutoxycarbonyl, benzoyl, 1-methylcyclohexanecarbonyl, 1-isopentylcyclopentanecarbonyl, 1-isopentylcyclohexanecarbonyl, and 2-(1-isopentylcyclohexanecarbonylamino)phenylthiocarbonyl.

[0041] The term "substituted or unsubstituted" of the "substituted or unsubstituted C_{3-10} cycloalkyl group", the "substituted or unsubstituted C_{5-8} cycloalkenyl group", and the "substituted or unsubstituted C_{3-10} cycloalkyl C_{1-10} alkyl group" described for R, R_1, and the like means that the group may be substituted with 1-4 substituents which may be the same or different and any position may be arbitrarily substituted without any limitation. Specific examples of these groups are the above-described straight chain or branched C_{1-10} alkyl group; the above-described straight chain or branched C_{2-10} alkenyl group; the above-described C_{3-10} cycloalkyl group; the above-described C_{5-8} cycloalkenyl group; the above-described C_{3-10} cycloalkyl C_{1-10} alkyl group; the above-described aryl group; an amino group; a C_{1-4} lower alkylamino group such as methylamino, ethylamino, or the like groups; an acylamino group such as acetylamino, propionylamino, benzylamino, or the like groups; an oxo group; the above-described aralkyl group; the above-described arylalkenyl group, and the like.

[0042] The above substituents are recommended as substituents for R. Among these, preferred for R_1 are the above-described straight chain or branched C_{1-10} alkyl group, the above-described C_{3-10} cycloalkyl group, the above-described C_{5-8} cycloalkenyl group, the above-described aryl group, and the above-described amino group.

[0043] The term "substituted or unsubstitueted" of the "substituted or unsubstitueted aryl group", the "5- or 6-membered heterocyclic group containing 1-3 nitrogen, oxygen, or sulfur atoms", the "substituted or unsubstitueted aralkyl group", the "substituted or unsubstitueted arylalkenyl group", the "substituted or unsubstitueted arylthio group", and the "substituted or unsubstitueted 5- or 6-membered heteroarylalkyl group" described with respect to R, R_1, and the like means that the groups may be substituted with 1-4, preferably 1-3, substituents which may be the same or different and any position may be arbitrarily substituted without particular restriction. Examples of these groups include the above-described straight chain or branched C_{1-10} alkyl group, preferably a straight chain or branched C_{1-6} aralkyl group; the above-described straight chain or branched C_{2-10} alkenyl group, preferably a straight chain or branched C_{2-6} alkenyl group; the above-described halogen atom; a nitro group; the above-described amino group that may be substituted with the above-described C_{1-4} lower alkyl group or the above-described acyl group; a hydroxyl group; the above-described C_{1-4} lower alkoxy group; the above-described C_{1-4} lower alkylthio group; the above-described halo-C_{1-4} lower alkyl group; the above-described acyl group; an oxo group, and the like.

[0044] The above substituents are recommended as substituents mainly for R_1. Among these, preferred for R the above-described straight chain or branched C_{1-6} alkyl group, the above-described halogen atom, and a nitro group.

[0045] The "substituted or unsubstituted" of the "substituted or unsubstituted straight chain or branched C_{1-10} alkyl group" described for R_1 and the like means that the group may be substituted with 1-3 substituents which may be the same or different and any position may be arbitrarily substituted without particular restriction. Examples of these groups are the above-described C_{1-4} lower alkoxy group; the above-described C_{1-4} lower alkyl group; the above-described amino group that may be substituted with an acyl or hydroxyl group; the above-described lower C_{1-4} alkylthio group; a carbamoyl group; a hydroxyl group; the above-described halogen atom; the above-described acyloxy group containing an acyl group; a carboxyl group; the above-described acyl group; the above-described aryloxy group containing an aryl group that may be substituted; and the like.

[0046] The "substituted or unsubstituted" of the "C_{1-4} lower alkyl group" described with respect to R_2 and the like means that the group may be substituted with 1-3 substituents which may be the same or different and any position may be arbitrarily substituted without particular restriction. Examples of the group include the above-described C_{1-4} lower alkoxy group; the above-described amino group that may be substituted with the above-described C_{1-4} lower alkyl group or the above-described acyl group; the above-described C_{1-4} lower alkylthio group; a carbamoyl group; a hydroxyl group; a carboxyl group; the above-described acyl group; the above-described heterocyclic group (particularly aromatic heterocyclic groups such as thienyl or non-aromatic heterocyclic group such as tetrahydrofuryl); and the like.

[0047] The term "substituted or unsubstituted" of the "substituted or unsubstituted amino group" and the "substituted or unsubstituted ureido group" described with respect to R_1 means that the groups may be substituted with one or more, preferably 1-2, substituents which may be the same or different and any position may be arbitrarily substituted without particular restriction. Examples of these groups are the above-described C_{1-4} lower alkyl group; a hydroxyl group; the above-described acyl group; the above-described aryl group which may be substituted with the above-described C_{1-4} lower alkoxy group; and the like.

[0048] The "mercapto-protecting group" described with respect to Z means commonly used mercapto protecting groups. Any organic residues that can be dissociated *in vivo* may be used without particular restriction. It may form a disulfide structure, that is dimer. Examples thereof include C_{1-4} lower alkoxymethyl; C_{1-4} lower alkylthiomethyl; aralkyloxymethyl; aralkylthiomethyl; C_{3-10} cycloalkyloxymethyl; C_{5-8} cycloalkenyloxymethyl; C_{3-10} cycloalkyl C_{1-10} alkoxymethyl; aryloxymethyl; arylthiomethyl; acyl; acyloxy; aminocarbonyloxymethyl; thiocarbonyl; and thio groups. Specific examples thereof include a C_{1-4} lower alkoxymethyl group with the above-described C_{1-4} lower alkoxy group; a C_{1-4} lower alkylthiomethyl group with the above-described C_{1-4} lower alkylthio group; an aralkyloxymethyl group with the above-described aralkyl group; an aralkylthiomethyl group with the above-described aralkyl group; a C_{3-10} cycloalkyloxymethyl group with the above-described C_{3-10} cycloalkyl group; a C_{5-8} cycloalkenyloxymethyl group with the above-described C_{5-8} cycloalkenyl group; a C_{3-10} cycloalkyl C_{1-10} alkoxymethyl group with the above-described C_{3-10} cycloalkyl C_{1-10} alkyl group; an aryloxymethyl group with the above-described aryl group; an arylthiomethyl group with the above-described arylthio group; an acyl group containing the above-described substituted or unsubstituted straight chain or branched C_{1-10} alkyl group, the above-described halo-C_{1-4} lower alkyl group, the above-described C_{1-4} lower alkoxy group, the above-described C_{1-4} lower alkylthio group, the above-described substituted or unsubstituted amino group, the above-described substituted or unsubstituted ureido group, the above-described substituted or unsubstituted C_{3-10} cycloalkyl group, the above-described substituted or unsubstituted C_{3-10} cycloalkyl C_{1-10} alkyl group, the above-described substituted or unsubstituted aryl group, the above-described substituted or unsubstituted aralkyl group, the above-described substituted or unsubstituted arylalkenyl group, the above-described substituted or unsubstituted arylthio group, the above-described substituted or unsubstituted 5- or 6-membered heterocyclic group with 1-3 nitrogen, oxygen, or sulfur atoms, or the above-described substituted or unsubstituted 5- or 6-membered heteroarylalkyl group; an acyloxy group containing the above-described substituted or unsubstituted straight chain or branched C_{1-10} alkyl group, the above-described halo-C_{1-4} lower alkyl group, the above-described C_{1-4} lower alkoxy group, the above-described C_{1-4} lower alkylthio group, the above-described substituted or unsubstituted amino group, the above-described substituted or unsubstituted ureido group, the above-described substituted or unsubstituted C_{3-10} cycloalkyl group, the above-described substituted or unsubstituted C_{3-10} cycloalkyl C_{1-10} alkyl group, the above-described substituted or unsubstituted aryl group, the above-described substituted or unsubstituted aralkyl group, the above-described substituted or unsubstituted arylalkenyl group, the above-described substituted or unsubstituted arylthio group, the above-described substituted or unsubstituted 5- or 6-membered heterocyclic group with 1-3 nitrogen, oxygen, or sulfur atoms, or the above-described substituted or unsubstituted 5- or 6-membered heteroarylalkyl group; an aminocarbonyloxymethyl group that may be substituted with the above-described substituted or unsubstituted straight chain or branched C_{1-10} alkyl group, the above-described halo-C_{1-4} alkyl group, the above-described C_{1-4} lower alkoxy group, the above-described C_{1-4} lower alkylthio group, the above-described substituted or unsubstitutedc C_{3-10} cycloalkyl group, the above-described substituted or unsubstituted C_{3-10} cycloalkyl C_{1-10} alkyl group, the above-described substituted or unsubstituted aryl group, the above-described substituted or unsubstituted aralkyl group, the above-described substituted or unsubstituted arylalkenyl group, the above-described substituted or unsubstituted 5- or 6-membered heterocyclic group with 1-3 nitrogen, oxygen, or sulfur atoms, or the above-described substituted or unsubstituted 5- or 6-membered heteroarylalkyl group; a thiocarbonyl group containing the above-described substituted or unsubstituted

straight chain or branched C_{1-10} alkyl group, the above-described halo-C_{1-4} lower alkyl group, the above-described C_{1-4} lower alkoxy group, the above-described C_{1-4} lower alkylthio group, the above-described substituted or unsubstituted amino group, the above-described substituted or unsubstituted ureido group, the above-described substituted or unsubstituted C_{3-10} cycloalkyl group, the above-described substituted or unsubstituted C_{3-10} cycloalkyl C_{1-10} alkyl group, the above-described substituted or unsubstituted aryl group, the above-described substituted or unsubstituted aralkyl group, the above-described substituted or unsubstituted arylalkenyl group, the above-described substituted or unsubstituted arylthio group, the above-described substituted or unsubstituted 5- or 6-membered heterocyclic group with 1-3 nitrogen, oxygen, or sulfur atoms, or the above-described substituted or unsubstituted 5- or 6-membered heteroarylalkyl group; and a thio group containing the above-described substituted or unsubstituted C_{1-4} lower alkyl or aryl group.

[0049] More specifically, preferred as the "straight chain or branched C_{1-10} alkyl group" for R are methyl, ethyl, isopropyl, butyl, isobutyl, tert-butyl, heptyl, 1-propylbutyl, and 1-isobutyl-3-methylbutyl.

[0050] The "straight chain or branched C_{2-10} alkenyl group" referred to as R are preferably allyl, vinyl, isopropenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, 1-methyl-1-butenyl, crotyl, 1,3-dimethyl-2-butenyl, 1-pentenyl, and 1-methyl-2-pentenyl.

[0051] The "halo-C_{1-4} lower alkyl group" for R means a C_{1-4} lower alkyl group, particularly preferably a methyl group, substituted with the above-described halogen atom, particularly preferably fluorine and chlorine, with being a trifluoromethyl group preferred.

[0052] The "substituted or unsubstituted C_{3-10} cycloalkyl group" for R means a C_{3-10} cycloalkyl group (particularly preferably cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, octahydroindenyl, decahydronaphthyl, adamantyl, and bicyclo[2.2.1]-heptyl)that may be substituted with 1-4 substituents selected from the above-described straight chain or branched C_{1-10} alkyl group, (particularly preferably a C_{1-8} alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl, 2,2-dimethylpropyl, 4-methylpentyl, 2-ethylbutyl, or the like), the above-described straight chain or branched C_{2-10} alkenyl group (particularly preferably a C_{2-8} alkenyl group such as 1-methylvinyl, 2-methylvinyl, 3-methyl-3-propenyl, or the like), the above-described C_{3-10} cycloalkyl group (particularly preferably a C_{3-7} cycloalkyl group such as cyclopropyl, cyclopentyl, cyclohexyl, or the like), the above-described C_{5-8} cycloalkenyl group (particularly preferably a C_{5-6} cycloalkenyl group such as cyclopentenyl, cyclohexenyl, or the like), the above-described C_{3-10} cycloalkyl C_{1-10} alkyl group (particularly preferably a C_{3-7} cycloalkyl C_{1-4} alkyl group such as cyclopropylmethyl, 2-cyclopropylethyl, 2-cyclopentylethyl, cyclohexylmethyl, 2-cyclohexylethyl, or the like), the above-described aryl group (particularly preferably a phenyl group), an oxo group, the above described aralkyl group (particularly preferably a phenyl C_{1-4} lower alkyl group such as benzyl, phenethyl, or the like), and the above-described arylalkenyl group (particularly preferably a 2-phenylvinyl group). Preferable examples thereof include 2,2,3,3-tetramethylcyclopropyl, 1-isopentylcyclobutyl, 1-isopropylcyclopentyl, 1-isobutylcyclopentyl, 1-isopentylcyclopentyl, 1-cyclohexylmethylcyclopentyl, cyclohexyl, 1-methylcyclohexyl, 1-ethylcyclohexyl, 1-propylcyclohexyl, 1-isopropylcyclohexyl, 1-butylcyclohexyl, 1-isobutylcyclohexyl, 1-pentylcyclohexyl, 1-isopentylcyclohexyl, 1-(2,2-dimethylpropyl)-cyclohexyl, 1-(4-methylpentyl)cyclohexyl, 1-(2-ethylbutyl) cyclohexyl, 4-tert-butyl-1-isopentylcyclohexyl, 1-cyclopropyl-cyclohexyl, 1-bicyclohexyl, 1-phenylcyclohexyl, 1-cyclopropylmethylcyclohexyl, 1-cyclohexylmethylcyclohexyl, 1-(2-cyclopropylethyl) cyclohexyl, 1-(2-cyclopentylethyl)cyclohexyl, 1-(2-cyclohexylethyl)cyclohexyl, 4-methylcyclohexyl, 4-propyl-cyclohexyl, 4-isopropylcyclohexyl, 4-tert-butylcyclohexyl, 4-pentylcyclohexyl, 4-bicyclohexyl, 1-isopentylcycloheptyl, 3a-octahydroindenyl, 4a-decahydronaphthyl, 1-adamantyl, and 7,7-dimethyl-1-(2-oxo)-bicyclo[2.2.1]heptyl. The site of substitution is not specifically limited, but particularly preferably at position 1. Any substitution group as described above may be used, but the straight chain or branched C_{1-10} alkyl group is particularly preferred.

[0053] The substituent for the "substituted or unsubstituted C_{5-8} cycloalkenyl group" for R is the same as that for the above "substituted or unsubstituted C_{3-10} cycloalkyl group". Specifically, it means a cycloalkenyl group (especially cyclopentenyl and cyclohexenyl) that may have 1-4 substituents selected from the above-described straight chain or branched C_{1-10} alkyl group (particularly preferably a C_{1-8} alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, isopentyl, 2,2-dimethylpropyl, 4-methylpentyl, or the like), the above-described straight chain or branched C_{2-10} alkenyl group (particularly preferably a C_{2-8} alkenyl group such as 1-methylvinyl, 2-methylvinyl, 3-methyl-3-propenyl, and the like), the above-described C_{3-10} cycloalkyl group (particularly preferably a C_{3-7} cycloalkyl group such as cyclopropyl, cyclopentyl, cyclohexyl, or the like), the above-described C_{5-8} cycloalkenyl group (particularly preferably a C_{5-6} cycloalkenyl group like cyclopentenyl, cyclohexenyl, or the like), the above-described C_{3-10} cycloalkyl C_{1-10} alkyl group (particularly preferably a C_{3-7} cycloalkyl C_{1-4} lower alkyl group such as cyclopropyl methyl, 2-cyclopropylethyl, 2-cyclopentylethyl, cyclohexylmethyl, 2-cyclohexylethyl, or the like), the above-described aryl group (particularly preferably a phenyl group), an oxo group, the above-described aralkyl group (particularly preferably a phenyl C_{1-4} lower alkyl group such as benzyl, phenethyl, or the like), and arylalkenyl group (particularly preferably 2-phenylvinyl). Preferable examples of the cycloalkenyl group includes 1-isopropyl-2-cyclopentenyl, 1-isopropyl-3-cyclopentenyl, 1-isobutyl-2-cyclopentenyl, 1-isobutyl-3-cyclopentenyl, 1-isopentyl-2-cyclopentenyl, 1-isopentyl-3-cyclopentenyl, 1-cyclohexylmethyl-2-cyclopentenyl, 1-cyclohexylmethyl-3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-methyl-2-cyclohexenyl, 1-methyl-3-cyclohexenyl, 1-ethyl-2-cyclohexenyl, 1-ethyl-3-cyclohexenyl, 1-propyl-2-cyclohexenyl, 1-pro-

pyl-3-cyclohexenyl, 1-isopropyl-2-cyclohexenyl, 1-isopropyl-3-cyclohexenyl, 1-butyl-2-cyclohexenyl, 1-butyl-3-cyclohexenyl, 1-isobutyl-2-cyclohexenyl, 1-isobutyl-3-cyclohexenyl, 1-pentyl-2-cyclohexenyl, 1-pentyl-3-cyclohexenyl, 1-isopentyl-2-cyclohexenyl, 1-isopentyl-3-cyclohexenyl, 1-(2,2-dimethylpropyl)-2-cyclohexenyl, 1-(2,2-dimethylpropyl)-3-cyclohexenyl, 1-(4-methylpentyl)-2-cyclohexenyl, 1-(4-methylpentyl)-3-cyclohexenyl, 1-cyclopropyl-2-cyclohexenyl, 1-cyclopropyl-3-cyclohexenyl, 1-cyclohexyl-2-cyclohexenyl, 1-cyclohexyl-3-cyclohexenyl, 1-phenyl-2-cyclohexenyl, 1-phenyl-3-cyclohexenyl, 1-cyclopropylmethyl-2-cyclohexenyl, 1-cyclo propylmethyl-3-cyclohexenyl, 1-cyclohexylmethyl-2-cyclohexenyl, 1-cyclohexylmethyl-3-cyclohexenyl, 1-(2-cyclopropylethyl)-2-cyclohexenyl, 1-(2-cyclopropylethyl)-3-cyclohexenyl, 1-(2-cyclopentylethyl)-2-cyclohexenyl, 1-(2-cyclopentylethyl)-3-cyclohexenyl, 1-(2-cyclohexylethyl)-2-cyclohexenyl, and 1-(2-cyclohexylethyl)-3-cyclohexenyl. There is no special restriction on the substitution position, but the particularly preferred position is position 1. Any one of the above substituents may be used, but the straight chain or branched C_{1-10} alkyl group or the C_{3-10} cycloalkyl C_{1-4} alkyl group is particularly preferred.

[0054] The "substituted or unsubstituted C_{3-10} cycloalkyl C_{1-10} alkyl group" for R means a C_{3-10} cycloalkyl C_{1-10} alkyl group (particularly preferably cyclohexylmethyl, 1-cyclohexylethyl, 1-cyclohexyl-1-methylethyl, 1-cyclohexyl-2-methylpropyl, 1-cyclohexyl-3-methylbutyl, 1-cyclohexylhexyl, 1-cyclohexyl-4-methylpentyl, and 1-cyclohexylheptyl) C_{1-10} alkyl group of which is straight chain or branched and which may have 1-4 substituents selected from the above-described C_{3-10} cycloalkyl group (particularly preferably a C_{3-7} cycloalkyl group such as cyclopentyl or cyclohexyl), the above-described C_{5-8} cycloalkenyl group (particularly preferably a C_{5-7} cycloalkenyl group such as cyclopentenyl or cyclohexenyl), and the above-described aryl group (particularly preferably a phenyl group). There is no special restriction on the substitution position. The above-described substituents may be placed at the straight chain or branched C_{1-10} alkyl moiety. Preferable examples of the C_{3-10} cycloalkyl C_{1-10} alkyl group include cyclohexylmethyl, 1-cyclohexylethyl, cyclohexylcyclo-pentylmethyl, dicyclohexylmethyl, 1-cyclohexyl-1-methylethyl, 1-cyclohexyl-2-methylpropyl, 1-cyclohexyl-3-methylbutyl, 1-cyclohexyl-4-methylpentyl, 1-cyclohexylhexyl, and 1-cyclohexylheptyl.

[0055] The "substituted or unsubstituted aryl group" for R means an aryl group (particularly preferably a phenyl group) that may have 1-4 substituents selected from the above-described straight chain or branched C_{1-6} alkyl group (particularly preferably a tert-butyl group), the above-described halogen atom (particularly preferably fluorine and chlorine), and a nitro group. Preferable examples of the aryl group are phenyl, 2-chlorophenyl, 4-nitrophenyl, and 3,5-di-tert-butylphenyl.

[0056] The "substituted or unsubstituted aralkyl" for R means an aralkyl group (particularly preferably benzyl, benzhydryl, and trityl) which may have substituents selected from the above-described halogen atom (particularly preferably fluorine and chlorine), a nitro group, and a hydroxy group, and in which the C_{1-4} lower alkyl group is straight chain or branched. There is no special restriction on the position of substitution. The straight chain or branched C_{1-4} lower alkyl moiety may be substituted. Preferable examples of the aralkyl group are benzyl and trityl.

[0057] The "substituted or unsubstituted 5- or 6-membered heterocyclic group having 1-3 nitrogen, oxygen or sulfur atoms" for R means the above-described heterocyclic group that may have 1-4 substituents selected from the above-described straight chain or branched C_{1-6} alkyl group (particularly preferably a tert-butyl group), the above-described halogen atom (particularly preferably fluorine and chlorine), and a nitro group. The heterocyclic group is preferably an aromatic heterocyclic group, particularly preferably furyl, thienyl, and pyridyl.

[0058] The " substituted or unsubstituted straight chain or branched C_{1-10} alkyl group" for R_1 means a straight chain or branched C_{1-10} alkyl group that may have a substituent selected from the above-described halogen atom (particularly preferably fluorine and chlorine), the above-described C_{1-4} lower alkoxy group (particularly preferably a methoxy group), an amino group that may be substituted with the above-described C_{1-4} lower alkyl group (particularly preferably a methyl group), the above-described acyl group (particularly preferably an acetyl group), or a hydroxyl group, the above-described C_{1-4} lower alkylthio group (particularly preferably a methylthio group), a carbamoyl group, a hydroxyl group, an acyloxy group having the above-described acyl group (particularly preferably an acetyloxy group), a carboxyl group, an acyl group (particularly preferably a methoxycarbonyl group), and an aryloxy group having the above-described substituted or unsubstituted aryl group (particularly preferably a phenoxy group and a 4-chlorophenoxy group). Preferable examples of the alkyl group include methyl, chloromethyl, ethyl, isopropyl, 1-methyl-2-pentyl, octyl, methoxymethyl, dimethylaminomethyl, acetylaminomethyl, 1-acetyl aminoethyl, 1-acetylamino-2-methylpropyl, 1-acetylamino-3-methylbutyl, 1-acetylamino-3-methylthiopropyl, 1-acetylamino-3-carbamoylpropyl, 1-hydroxy-1-methylethyl, 1-acetyloxy-1-methylethyl, 4-carboxybutyl, 2-methoxycarbonylethyl, phenoxymethyl, and 4-chlorophenoxymethyl.

[0059] The "C_{1-4} lower alkoxy group" for R_1 is preferably a methoxy group and a tert-butoxy group.

[0060] The "C_{1-4} lower alkylthio group" for R_1 is preferably a methyl-thio group.

[0061] The "substituted or unsubstituted amino group" for R_1 means an amino group that may have a substituent selected from the above-described C_{1-4} lower alkyl group (particularly preferably ethyl, isopropyl, and tert-butyl), the above-described acyl group (particularly preferably acetyl and benzoyl), and the above-described aryl group (particularly preferably phenyl and 4-methoxyphenyl) that may be substituted with the above-described C_{1-4} lower alkoxy group. Preferable examples of the amino group are ethylamino, isopropylamino, tert-butylamino, phenylamino, and 4-methoxyphenylamino.

[0062] The "substituted or unsubstituted ureido group" for R_1 means a ureido group that may have a substituent selected from the above-described C_{1-4} lower alkyl group (particularly preferably methyl and ethyl), the above-described acyl group (particularly preferably acetyl and benzoyl), and the above-described aryl group (particularly preferably phenyl and 4-methoxyphenyl) that may be substituted with the above-described C_{1-4} lower alkoxy group, with an N,N'-diphenylureido group being preferred.

[0063] The "substituted or unsubstituted C_{3-10} cycloalkyl group" for R_1 means a C_{3-10} cycloalkyl group (particularly preferably cyclopropyl and cyclohexyl) that may have a substituent selected from the above-described straight chain or branched C_{1-10} alkyl group (particularly preferably methyl, tert-butyl, and isopentyl), an amino group, an amino group (particularly preferably methylamino, ethylamino, acetylamino, and benzylamino) that may be substituted with the above-described C_{1-4} lower alkyl or acyl groups. Preferable examples the cycloalkyl group are cyclopropyl, cyclohexyl, 1-methylcyclohexyl, 1-isopentylcyclohexyl, 1-aminocyclohexyl, 1-acetylaminocyclohexyl, and 4-tert-butylcyclohexyl.

[0064] The "substituted or unsubstituted C_{3-10} cycloalkyl C_{1-10} alkyl group" for R_1 means a C_{3-10} cycloalkyl C_{1-10} alkyl group which may have a substituent selected from the above-described C_{3-10} cycloalkyl group (particularly preferably cyclopentyl and cyclohexyl), the above-described C_{5-8} cycloalkenyl group (particularly preferably cyclopentenyl and cyclohexenyl), and the above-described aryl group (particularly preferably a phenyl group) and in which the C_{1-10} alkyl moiety is straight chain or branched. There is no special restriction on the position of substitution. The straight chain or branched C_{1-10} alkyl moiety may be substituted. A cyclohexylmethyl group is preferred as the C_{3-10} cycloalkyl C_{1-10} alkyl group.

[0065] The "substituted or unsubstituted aryl group " for R_1 means an aryl group (particularly preferably phenyl and naphthyl) that may have a substituent selected from the above-described straight chain or branched C_{1-6} alkyl group (particularly preferably methyl and tert-butyl group), the above-described halogen atom (particularly preferably fluorine and chlorine), a nitro group, a hydroxyl group, the above-described C_{1-4} lower alkoxy group (particularly preferably a methoxy group), and the above-described acyl group (particularly preferably a 2-(1-isopentylcyclohexanecarbonylamino)phenylthiocarbonyl group). Preferable examples of the aryl group include phenyl, 1-naphthyl, 2-naphthyl, 2-chlorophenyl, 2,6-dichlorophenyl, 2,6-dimethyiphenyl, 2-methoxyphenyl, 2-nitrophenyl, 4-nitrophenyl, 3,5-di-tert-butyl-4-hydroxyphenyl, and 4-[2-(1-isopentylcyclohexanecarbonylamino)phenylthiocarbonyl]phenyl.

[0066] The "substituted or unsubstituted aralkyl group " for R_1 means an aralkyl group (particularly preferably benzyl, phenethyl, 3-phenylpropyl, naphthylmethyl, and biphenylmethyl) that may have a substituent selected from the above-described halogen atom (particularly preferably fluorine and chlorine), a nitro group, an amino group (particularly preferably amino, acetylamino, pivaloylamino, 1-methylcyclohexanecarbonyl-amino, tert-butoxycarbonylamino, and benzoylamino) that may be substituted with the above-described C_{1-4} lower alkyl group or the above-described acyl group ,and a hydroxyl group, and in which the C_{1-4} lower alkyl group are straight chain or branched. There is no special restriction on the position of substitution. The straight chain or branched C_{1-4} lower alkyl moiety may be substituted. Preferable examples of the aralkyl group include benzyl, phenethyl, 3-phenylpropyl, 2-naphthylmethyl, 4-biphenylmethyl, benzhydryl, 2-chlorophenylmethyl, 3-chloro phenylmethyl, 4-chlorophenylmethyl, 2-nitrophenylmethyl, 4-nitrophenylmethyl, 2-pivaloylaminophenylmethyl, 2-(1-methylcyclohexanecarbonylamino)phenylmethyl, 2-tert-butoxycarbonylaminophenylmethyl, 3-acetylaminophenylmethyl, 3-(1-methylcyclohexanecarbonylamino)phenylmethyl, α-aminobenzyl, α-acetylaminobeozyl, α-(1-methylcyclohexanecarbonylamino)benzyl, α-benzoylaminobenzyl, α-aminophenethyl, α-acetylaminophenethyl, and 1-acetylamino-2-(4-hydorxyphenyl) ethyl.

[0067] The "substituted or unsubstituted arylalkenyl group" for R_1 means an arylalkenyl group (particularly phenylvinyl) that may have a substituent selected from the above-described straight chain or branched C_{1-6} lower alkyl group (particularly preferably methyl and tert-butyl), the above-described halogen atom (particularly preferably fluorine and chlorine), a nitro group, and a hydroxyl group, with a 2-phenylvinyl group being preferred.

[0068] The "substituted or unsubstituted arylthio group" for R_1 means an arylthio group (particularly preferably a phenylthio group) that may have a substituent selected from the above-described halogen atom (particularly preferably fluorine and chlorine), a nitro group, and an amino group that may be substituted with the above-described C_{1-4} lower alkyl group or the above-described acyl group (particularly preferably amino, acetylamino, pivaloylamino, 1-methylcyclohexanecarbonylamino, and benzoylamino), a hydroxyl group, and the above-described halo-C_{1-4} lower alkyl group (particularly preferably a trifluoromethyl group). Preferably examples of the arylthio group include phenylthio, 2-pivaloylaminophenylthio, 2-(1-methylcyclohexanecarbonylamino)phenylthio, and 2-(1-methyl cyclohexanecarbonylamino-4-trifluoromethyl)phenylthio.

[0069] The "substituted or unsubstituted 5- or 6-membered heterocyclic ring groups with 1-3 nitrogen, oxygen, or sulfur atoms" for R_1 means heterocyclic ring groups (particularly preferably an aromatic heterocyclic group such as pyridyl or a non-aromatic heterocyclic group such as piperidyl or pyrrolidinyl) that may have substituents selected from the above-described straight chain or branched C_{1-6} alkyl group (particularly preferably a methyl group), a halogen atom (particularly preferably fluorine and chlorine), the above-described acyl group (particularly preferably acetyl and benzoyl), and an oxo group. Preferable examples thereof are 3-pyridyl, 1-methyl-4-piperidyl, 1-acetyl-4-piperidyl, 5-oxo-2-pyrrolidinyl, 1-acetyl-2-pyrrolidinyl, and 1-benzoyl-2-pyrrolidinyl. A 4-piperidyl group such as 1-methyl-4-piperidyl or 1-

acetyl-4-piperidyl group is particularly preferred.

[0070] The "substituted or unsubstituted 5- or 6-membered heteroarylalkyl group" for R_1 means the above-described heteroarylalkyl group (particularly preferably a 2-tenyl group) that may be substituted with the above-described straight chain or branched C_{1-6} alkyl group (particularly preferably a methyl group) and the above-described halogen atom (particularly preferably fluorine and chlorine). A 2-tenyl group is preferred.

[0071] The "substituted or unsubstituted C_{1-4} lower alkyl group" for R_2 means a C_{1-4} lower alkyl group (particularly preferably a methyl group) that may have 1-3 substituents selected from the above-described C_{1-4} lower alkoxy group (particularly preferably a methoxy group), an amino group that may be substituted with the above-described C_{1-4} lower alkyl or acyl group (particularly preferably a dimethylamino group), the above-described C_{1-4} lower alkylthio group (particularly preferably a methylthio group), a carbamoyl group, a hydroxyl group, a carboxyl group, the above-described acyl group (particularly preferably a methoxycarbonyl group), and the above-described heterocyclic group (particularly preferably an aromatic heterocyclic group such as thienyl or a non-aromatic heterocyclic group such as tetrahydrofuryl). A tetrahydrofurylmethyl group is preferred.

[0072] The "substituted or unsubstituted aryl group" for R_2 is the same as that for R_1. Preferable examples thereof are a phenyl group, a halogenated phenyl group, an acylamino-substituted phenyl group, and the like.

[0073] The "halogen atom" for X_1, X_2, X_3, and X_4 means a halogen atom including fluorine, chlorine, bromine, and the like, with fluorine and chlorine being preferred.

[0074] The "C_{1-4} lower alkyl group" for X_1, X_2, X_3, and X_4 is preferably a methyl group.

[0075] The "halo-C_{1-4} lower alkyl group" for X_1, X_2, X_3, and X_4 means a C_{1-4} lower alkyl group (particularly preferably a methyl group) substituted with the above-described halogen atom (particularly preferably fluorine and chlorine). A trifluoromethyl group is preferred.

[0076] The "C_{1-4} lower alkoxy group" for X_1, X_2, X_3, and X_4 is preferably a methoxy group.

[0077] The "acyl group" for X_1, X_2, X_3, and X_4 is preferably a benzoyl group.

[0078] The "aryl group" for X_1, X_2, X_3, and X_4 is preferably a phenyl group.

[0079] The "1-substituted-C_{3-10} cycloalkyl group" for R" means a cycloalkyl group (for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, preferably a C_{5-7} cycloalkyl group, particularly preferably a cyclohexyl group) that is substituted at position 1 with substituents selected from the above-described straight chain or branched C_{1-10} alkyl group (particularly preferably a C_{1-8} alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, isopentyl, 2,2-dimethylpropyl, 4-methylpentyl, or 2-ethylbutyl), the above-described straight chain or branched C_{2-10} alkenyl group (particularly preferably a C_{2-8} alkenyl group such as 1-methylvinyl, 2-methylvinyl, or 3-methyl-3-propenyl), the above-described C_{3-10} cycloalkyl (particularly preferably a C_{3-7} cycloalkyl group such as cyclopropyl, cyclopentyl, or cyclohexyl), the above-described C_{5-8} cycloalkenyl group (particularly preferably a C_{5-6} cycloalkenyl group such as cyclopentenyl or cyclohexenyl), the above-described C_{3-10} cycloalkyl C_{3-10} alkyl group (particularly preferably a C_{3-7} cycloalkyl C_{1-4} lower alkyl group such as cyclopropylmethyl, 2-cyclopropylethyl, 2-cyclopentylethyl, cyclohexylmethyl, or 2-cyclohexylethyl), the above-described aryl group (particularly preferably a phenyl group), the above-described aralkyl group (particularly preferably a phenyl C_{1-4} lower alkyl group such benzyl and phenethyl), and an arylalkenyl group (particularly preferably 2-phenylvinyl). Preferable examples of the 1-substituted-C_{3-10} cycloalkyl group include 1-isopentylcyclobutyl, 1-isopropylcyclopentyl, 1-isobutylcyclopentyl, 1-isopentyl cyclopentyl, 1-cyclohexylmethylcyclopentyl, 1-methylcyclohexyl, 1-ethylcyclohexyl, 1-propylcyclohexyl, 1-isopropylcyclohexyl, 1-butylcyclohexyl, 1-isobutylcyclohexyl, 1-pentylcyclohexyl, 1-isopentylcyclohexyl, 1-(2,2-dimethyipropyl)cyclohexyl, 1-(4-methylpentyl)cyclohexyl, 1-(2-ethylbutyl)cyclohexyl, 1-cyclopropylcyclohexyl, 1-bicyclohexyl, 1-phenylcyclohexyl, 1-cyclopropylmethylcyclohexyl, 1-cyclohexylmethylcyclohexyl, 1-(2-cyclopropylethyl)cyclohexyl, 1-(2-cyclopentylethyl)cyclohexyl, 1-(2-cyclohexylethyl)cyclohexyl, and 1-isopentylcycloheptyl. The straight chain or branched C_{1-10} alkyl group is particularly preferable as a substituent at position 1.

[0080] The "1-substituted-C_{5-8} cycloalkenyl group" for R" means a cycloalkenyl groups (particularly preferably a C_{5-6} cycloalkenyl group such as cyclopentenyl or cyclohexenyl) that is substituted at position 1 with substituents selected from the above-described straight chain or branched C_{1-10} alkyl group (particularly preferably a C_{1-8} alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, isopentyl, 2,2-dimethyl propyl, and 4-methylpentyl), the above-described straight chain or branched C_{2-10} alkenyl group (particularly preferably a C_{2-8} alkenyl group such as 1-methylvinyl, 2-methylvinyl, or 3-methyl-3-propenyl), the above-described C_{3-10} cycloalkyl group (particularly preferably a C_{3-7} cycloalkyl group such as cyclopropyl, cyclopentyl, or cyclohexyl), the above-described C_{5-8} cycloalkenyl group (particularly preferably a C_{5-6} cycloalkenyl group such as cyclopentenyl or cyclohexenyl), the above-described C_{3-10} cycloalkyl C_{1-10} alkyl group (particularly preferably a C_{3-7} cycloalkyl C_{1-4} lower alkyl group such as cyclopropylmethyl, 2-cyclopropylethyl, 2-cyclopentylethyl, cyclohexylmethyl, or 2-cyclohexylethyl), the above-described aryl group (particularly preferably a phenyl group), the above-described aralkyl group (particularly preferably a phenyl C_{1-4} lower alkyl group such as benzyl or phenethyl), and the above-described arylalkenyl group (particularly preferably a 2-phenylvinyl group). Preferable examples of the 1-substituted-C_{5-8} cycloalkenyl group include 1-isopropyl-2-cyclopentenyl, 1-isopropyl-3-cyclopentenyl, 1-isobutyl-2-cyclopentenyl, 1-isobutyl-3-cyclopentenyl, 1-isopentyl-2-cyclopentenyl, 1-isopentyl-3-

cyclopentenyl, 1-cyclohexylmethyl-2-cyclopentenyl, 1-cyclohexylmethyl-3-cyclopentenyl, 1-methyl-2-cyclohexenyl, 1-methyl-3-cyclohexenyl, 1-ethyl-2-cyclohexenyl, 1-ethyl-3-cyclohexenyl, 1-propyl-2-cyclohexenyl, 1-propyl-3-cyclohexenyl, 1-isopropyl-2-cyclohexenyl, 1-isopropyl-3-cyclohexenyl, 1-butyl-2-cyclohexenyl, 1-butyl-3-cyclohexenyl, 1-isobutyl-2-cyclohexenyl, 1-isobutyl-3-cyclohexenyl, 1-pentyl-2-cyclohexenyl, 1-pentyl-3-cyclohexenyl, 1-isopentyl-2-cyclohexenyl, 1-isopentyl-3-cyclohexenyl, 1-(2,2-dimethylpropyl)-2-cyclohexenyl, 1-(2,2-dimethylpropyl)-3-cyclohexenyl, 1-(4-methylpentyl)-2-cyclohexenyl, 1-(4-methylpentyl)-3-cyclohexenyl, 1-cyclopropyl-2-cyclohexenyl, 1-cyclopropyl-3-cyclohexenyl, 1-cyclohexyl-2-cyclohexenyl, 1-cyclohexyl-3-cyclohexenyl, 1-phenyl-2-cyclohexenyl, 1-phenyl-3-cyclohexenyl, 1-cyclopropylmethyl-2-cyclohexenyl, 1-cyclopropylmethyl-3-cyclohexenyl, 1-cyclohexylmethyl-2-cyclohexenyl, 1-cyclohexylmethyl-3-cyclohexenyl, 1-(2-cyclopropylethyl)-2-cyclohexenyl, 1-(2-cyclopropylethyl)-3-cyclohexenyl, 1-(2-cyclopentylethyl)-2-cyclohexenyl, 1-(2-cyclopentylethyl)-3-cyclohexenyl, 1-(2-cyclohexylethyl)-2-cyclohexenyl, and 1-(2-cyclohexylethyl)-3-cyclohexenyl. The straight chain or branched C_{1-10} alkyl group is particularly preferable as a substituent at position 1.

[0081] The "prodrug compound" means the derivatives of compounds of the present invention having a chemically or metabolically degradable group, which exhibit pharmaceutical activity by degradation through hydrolysis or solvolysis, or under physiological conditions.

[0082] The "pharmaceutically acceptable salt" means any compound that is an atoxic salt formed with the compound represented by the above formula (I). Examples of such a salt include inorganic acid salts such as hydrochlorides, hydrobromides, hydroiodides, sulfates, nitrates, phosphates, carbonates, bicarbonates, or perchlorates; organic acid salts such as formates, acetates, trifluoroacetates, propionates, tartrates, glycolates, succinates, lactates, maleates, hydroxymaleates, methylmaleates, fumarates, adipiates, tartrates, malates, citrates, benzoates, cinnamates, ascorbates, salicylates, 2-acetoxybenzoates, nicotinates, or isonicotinates; sulfonates such as methane sulfonates, ethane sulfonates, isethionates, benzene sulfonates, p-toluene sulfonates, or naphthalene sulfonates; salts of acidic amino acids such as aspargates or glutamates; alkali metal salts such as sodium salts or potassium salts, alkaline earth metal salts such as magnesium salts or calcium salts; ammonium salts; organic base salts such as trimethylamines, triethylamines, pyridine salts, picoline salts, dicyclohexylamine salts or N,N'-dibenzyl ethylenediamine salts; and salts of amino acids such as lysine salts or arginine salts. Depending on the circumstances, hydrates or solvates with alcohols may be used.

[0083] More specifically, a 1-isobutylcyclohexyl group, a 1-(2-ethylbutyl) cyclohexyl group, and a 1-isopentylcyclohexyl group are particularly preferable as R in the formula (I), -CO- is particularly preferable as Y, a hydrogen atom is particularly preferable as X_1, X_2, X_3, and X_4, and an isobutyryl group and a 1-acetyl-4-piperidine carbonyl group are particularly preferable as Z.

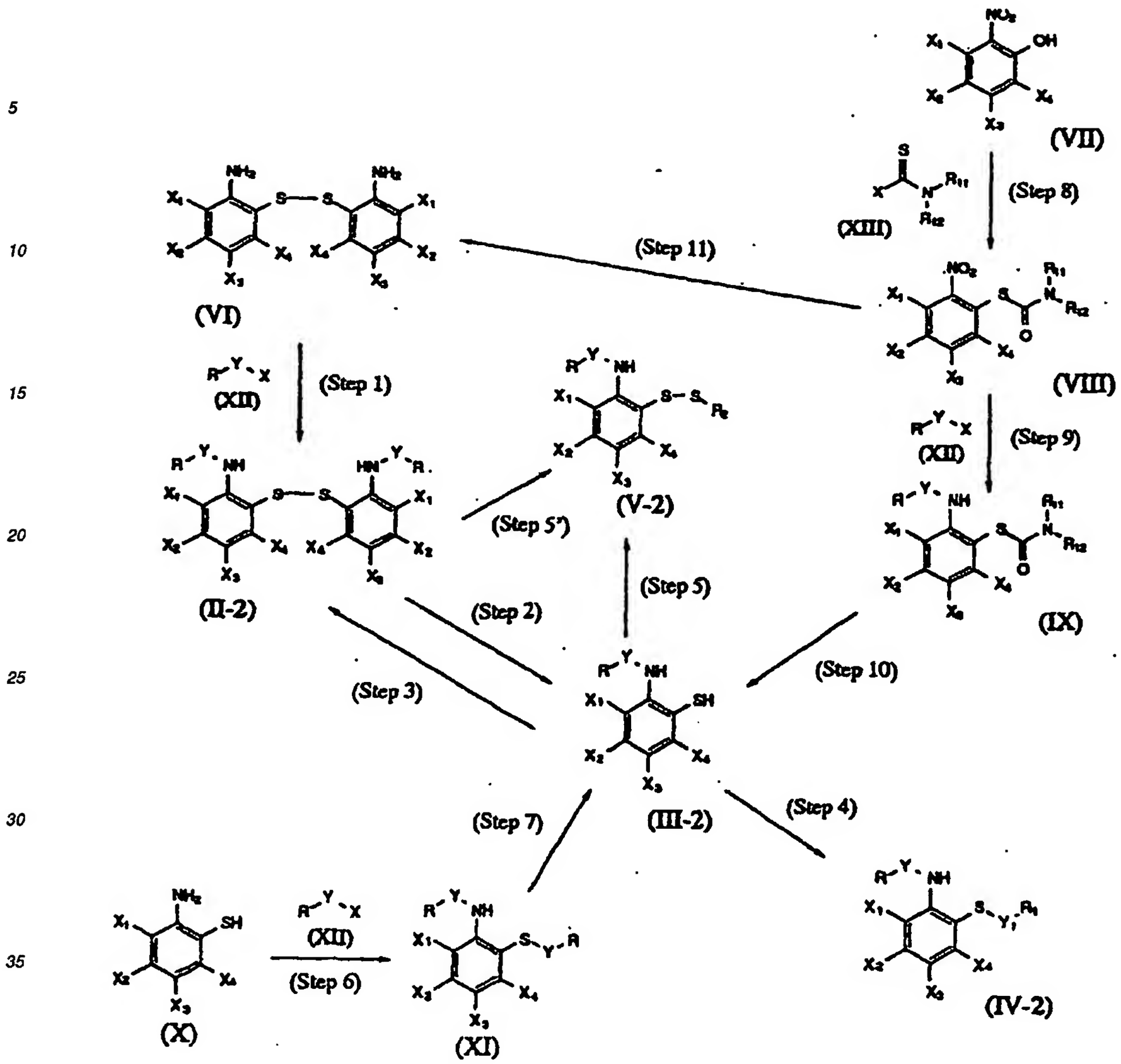
[0084] The compound of the present invention inhibits CETP activity and is expected as a conventionally unknown, new type of a preventive or therapeutic agent for hyperlipidemia or atherosclerotic diseases.

[0085] When used as a pharmaceutical preparation, the compound of the present invention represented by the formula (I) or a pharmaceutically acceptable salt thereof can be usually used together with known pharmacologically acceptable carriers, excipients, diluents, extenders, disintegrators, stabilizers, preservatives, buffers, emulsifiers, aromatics, colorants, sweeteners, viscosity increasing agents, flavor improving agents, solubilizers, and other additives. More specifically, the compound can be formulated into dosage forms, such as tablets, pills, powders, granules, suppositories, injections, eye drops, liquid drugs, capsules, troches, aerosols, elixirs, suspensions, emulsions, or syrup, together with water, plant oil, alcohols such as ethanol or benzyl alcohol, polyethylene glycol, glyceroltriacetate gelatin, lactose, carbohydrates such as starch, magnesium stearates, talc, lanolin, and vaseline, which can be administered orally or parenterally.

[0086] The above pharmaceutical preparations contain the compound of the present invention represented by the formula (I) or a pharmaceutically acceptable salt thereof in an amount effective to inhibit CETP activity and prevent or treat hyperlipidemia, atherosclerotic diseases, or the like diseases attributable to CETP activity. One skilled in the art can easily determine such an effective amount.

[0087] Doses may vary depending on the type and degree of diseases, the compounds to be administered, the route of administration, the age, sex, and body weight of the patients. In the case of oral administration, it is usually desirable to administer the compound (I) to an adult 1-1000 mg, particularly 50-800 mg per day.

[0088] The compound of the present invention can be produced using the following method, but it is needless to say that the method of producing the compound of the present invention is not limited to this method.



[Step 1]

[0089] The compound (II-2) (in the formula R, X_1, X_2, X_3, X_4, and Y are as described above) can be synthesized by reacting the compound (VI) (in the formula X_1, X_2, X_3 and X_4 are as described above) with the compound (XII) (in the formula X represents a halogen atom and R and Y are as described above) in the presence of a base such as pyridine, triethylamine, N-methylmorpholine, or N-methylpiperazine in an organic solvent such as methylene chloride, chloroform, toluene, ether, tetrahydrofuran, dioxane, diisopropyl ether, dimethoxyethane, or hexane, water, or a mixture of these solvents, or in the absence of a solvent, under cooling through heating temperature.

[0090] The compound (III-2) can be synthesized from the compound (II-2) by the following step 2.

[Step 2]

[0091] The compound (III-2) (in the formula R, X_1, X_2, X_3, X_4 and Y are as described above) can be synthesized by allowing the compound (II-2) (in the formula R, X_1, X_2, X_3, X_4 and Y are as described above) to react in the presence of a reducing agent such as sodium borohydride, lithium borohydride, aluminum lithium hydride, triphenylphosphine, zinc, or tin, in an organic solvent such as methanol, ethanol, ether, dioxane, tetrahydrofuran, diisopropyl ether, dimeth-

oxyethane, toluene, hexane, acetone, or acetic acid, water, or a mixture of these solvents, under cooling through heating temperature.

[0092] The compound (II-2) or (IV-2) can also be synthesized from the compound (III-2) using the following step 3 or 4.

[Step 3]

[0093] The compound (II-2) (in the formula R, X_1, X_2, X_3, X_4 and Y are as described above) can be synthesized by allowing the compound (III-2) (in the formula R, X_1, X_2, X_3, X_4 and Y are as described above) to react in the presence of an oxidizing agent such as iodine, hydrogen peroxide, potassium permanganate, or dimethylsulfoxide, in an organic solvent such as methanol, ethanol, ether, dioxane, tetrahydrofuran, diisopropyl ether, dimethoxyethane, acetone, toluene, hexane, dimethylformamide, or acetic acid, water, or a mixture of these solvents, or in the absence of a solvent, under cooling through heating temperature.

[Step 4]

[0094] The compound (IV-2) (in the formula R, R_1, X_1, X_2, X_3, X_4, Y, and Y_1 are as described above) can be synthesized by reacting the compound (III-2) (in the formula R, X_1, X_2, X_3, X_4, and Y are as described above) with acid halide R_1-YX (in the formula R_1, X, and Y are as described above), isocyanate R_1-NY (in the formula R_1 and Y are as described above), carbonic halide R_1-O-YX (in the formula R_1, X, and Y are as described above), or thiocarbonic halides R_1-S-YX (in the formula R_1, X and Y are as described above) in the presence of a base such as pyridine, triethylamine, N-methylmorpholine, or N-methylbipiperazine, in an organic solvent such as methylene chloride, chloroform, toluene, ether, dioxane, tetrahydro furan, diisopropyl ether, dimethoxy ethane, or hexane, water, or a mixture of these solvents, or in the absence of a solvent, under cooling through heating temperature. Alternatively, the compound (IV-2) can be synthesized by reacting the compound (III-2) with carboxylic acid R_1-COOH (in the formula R_1 is as described above) or thiocarboxylic acid R_1-YSH (in the formula R_1 and Y are as described above) using a coupling agent such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, dicyclohexylcarbodiimide, diphenylphosphorylazide, or carbonyldiimidazole, in the presence of an activating agent, if required, such as 1-hydroxybenzotriazole, hydroxysuccinimide, or N-hydroxy-5-norbornene-2,3-dicarboxylic acid imide, in an organic solvent such as dimethylformamide, dichloromethane, chloroform, acetonitrile, tetrahydrofuran, dimethylsufoxide, carbon tetrachloride, or toluene, or a mixture of these solvents, under cooling through heating temperature. (The reaction may be carried out in the presence of a base such as pyridine or triethylamine.) Furthermore, the compound (IV-2) can be synthesized by reacting the compound (III-2) with carboxylic acid R_1-COOH (in the formula R_1 is as described above) in the presence of a base such as triethylamine or pyridine and in the presence of ethyl chlorocarbonate or the like, in a organic solvent such as ethyl acetate or tetrahydrofuran, or a mixture of these solvents, under cooling through heating temperature. When R_1 has a carboxyl group, this above step may be conducted using the corresponding ester to obtain the compound by hydrolysis with acid using the known method.

[0095] The compound (IV-2) can also be synthesized by subsequently conducting the step 4 following the above step 2 or the step 7 below, or the step 10 below, without isolating the compound (III-2).

[0096] The compound (V-2) can be synthesized by conducting the following step 5 or 5'. The step 5 is suitable especially when R_2 is the lower alkyl group that may have substituents and the step 5' is suitable especially when R_2 is the aryl group that may have substituents.

[Step 5]

[0097] The compound (V-2) (in the formula R, R_2, X_1, X_2, X_3, X_4,and Y are as described above) can be synthesized by allowing R_2-X (in the formula R_2 and X is as described above) and a sulfur compound like sodium thiosulfate to react in an organic solvent such as ethanol, methanol, tetrahydrofuran, dioxane, dimethoxyethane, acetone, or acetonitrile, water, or a mixture of these solvents, at room temperature through heating temperature, and adding the compound (III-2) (in the formula R, X_1, X_2, X_3, X_4, and Y are as described above) and a basic aqueous solution such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, or sodium bicarbonate to the resulting solution under ice-cooling through heating temperature.

[Step 5']

[0098] The compound (V-2) (in the formula R, R_2, X_1, X_2, X_3, X_4, and Y are as described above) can be synthesized by reacting R_2-SH (in the formula R_2 is as described above) with trimethylsilane-imidazole in carbon tetrachloride under ice-cooling through room temperature, adding to the resulting solution a reaction mixture resulted from reacting the

compound (II-2) (in the formula R, X_1, X_2, X_3, X_4, and Y are as described above) with sulfuryl chloride in carbon tetrachloride in the presence of a base such as triethylamine, pyridine, N-methylmorpholine, or N-methylpiperazine under ice-cooling through room temperature, and allowing the resulting mixture to react.

[0099] The compound (III-2) can also be synthesized using the following scheme.

[Step 6]

[0100] The compound (XI) (in the formula R, X_1, X_2, X_3, X_4, and Y are as described above) can be synthesized by reacting the compound (X) (in the formula X_1, X_2, X_3, and X_4 are as described above) with the compound (XII) (in the formula R, X, and Y are as described above) in the presence of a base such as pyridine, triethylamine, N-methylmorpholine, or N-methylpiperazine, in an organic solvent such as methylene chloride, chloroform, toluene, ether, dioxane, tetrahydrofuran, diisopropyl ether, dimethoxyethane, or hexane, water, or a mixture of these solvents, or in the absence of a solvent, under cooling through heating temperature.

[Step 7]

[0101] The compound (III-2) (in the formula R, X_1, X_2, X_3, X_4, and Y are as described above) can be synthesized by allowing the compound (XI) (in the formula R, X_1, X_2, X_3, X_4, and Y are as described above) to react in the presence of a base such as sodium acetate, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, or sodium bicarbonate, in an organic solvent such as methanol, ethanol, tetrahydrofuran, dioxane, dimethoxyethane, ether, or diisopropyl ether, water, or a mixture of these solvents, under ice-cooling through heating temperature.

[0102] The compound (III-2) can also be synthesized by the following scheme.

[Step 8]

[0103] The compound (VIII) (in the formula R_{11} and R_{12} may be the same or different and are a lower alkyl group such as methyl or ethyl, and X_1, X_2, X_3, and X_4 are as described above) can be synthesized by reacting the compound (VII) (in the formula X_1, X_2, X_3, and X_4 are as described above) with the compound (XIII) (in the formula R_{11}, R_{12}, and X are as described above) in the presence of a base such as sodium hydride, triethylamine, or N-methylmorpholine, in an organic solvent such as dimethylformamide, tetrahydrofuran, dioxane, or dimethoxyethane or a mixture of these solvents, under cooling through heating temperature, and allowing the resulting product to react in an organic solvent such as phenylether or sulfolane or a mixture of these solvents, or in the absence of a solvent, under heating.

[Step 9]

[0104] The compound (IX) (in the formula R, R_{11}, R_{12}, X_1, X_2, X_3, X_4, and Y are as described above) can be synthesized by allowing the compound (VIII) (in the formula R_{11}, R_{12}, X_1, X_2, X_3, and X_4 are as described above) to react in the presence of a reducing agent such as stannous chloride, zinc, iron, sodium dithionite, sodium sulfide, or sodium disulfide, in an organic solvent such as ethyl acetate, acetic acid, methanol, ethanol, tetrahydrofuran, dioxane, diisopropyl ether, dimethoxyethane, or toluene, water, or a mixture of these solvents, under cooling through heating temperature, and reacting the resulting product with the compound (XII) (in the formula R, X, and Y are as described above) in the presence of a base such as pyridine, triethylamine, N-methylmorpholine, or N-methylpiperazine, in an organic solvent such as chloroform, methylene chloride, tetrahydrofuran, ether, dioxane, diisopropyl ether, dimethoxyethane, toluene, or hexane, water or a mixture of these solvents, or in the absence of a solvent, under cooling through heating temperature.

[Step 10]

[0105] The compound (III-2) (in the formula R, X_1, X_2, X_3, X_4, and Y are as described above) can be synthesized by allowing the compound (IX) (in the formula R, R_{11}, R_{12}, X_1, X_2, X_3, X_4, and Y are as described above) to react in the presence of a base such as potassium hydroxide, sodium hydroxide, potassium carbonate, sodium carbonate, or sodium bicarbonate, in an organic solvent such as methanol, ethanol, tetrahydrofuran, dioxane, dimethoxyethane, ether, or diisopropyl ether, water, or a mixture of these solvents, under cooling through heating temperature.

[0106] The compound (VI) can also be synthesized from the compound (VIII) by the following step 11.

[Step 11]

[0107] The compound (VI) (in the formula X_1, X_2, X_3, and X_4 are as described above) can be synthesized by allow-

ing the compound (VIII) (in the formula R_{11}, R_{12}, X_1, X_2, X_3, and X_4 are as described above) to react in the presence of a reducing agent such as stannous chloride, zinc, iron, sodium dithionite, sodium sulfide, and sodium disulfide, in an organic solvent such as ethyl acetate, acetic acid, methanol, ethanol, ether, tetrahydrofuran, dioxane, diisopropyl ether, dimethoxyethane, and toluene, water or a mixture at these solvents, under cooling through heating temperature, allowing the resulting product to react in the presence of a base such as potassium hydroxide, sodium hydroxide, potassium carbonate, sodium carbonate, or sodium bicarbonate, in an organic solvents such as methanol, tetrahydrofuran, ethanol, dioxane, ether, diisopropyl ether, or dimethoxyethane, water, or a mixture of these solvents, under cooling through heating temperature, and allowing the product to react in the presence of an oxidizing agent such as iodine, hydrogen peroxide, potassium permanganate, or dimethylsufoxide, in an organic solvent such as methanol, ethanol, ether, dioxane, tetrahydrofuran, diisopropyl ether, dimethoxyethane, acetone, toluene, hexane, dimethylformamide, or acetic acid, water, or a mixture of these solvents, or in the absence of a solvent, under cooling through heating temperature.

[0108] The compound (I) thus obtained can be isolated and purified using the known method for separation and purification, such as concentration, concentration under reduced pressure, extraction, crystallization, recrystallization, or chromatography.

[0109] The compound of the present invention contains one or more of stereoisomers due to the presence of the asymmetric carbon. Such isomers and mixtures thereof are all included in the scope of the present invention.

Best Mode for Carrying out the Invention

[0110] In the following the present invention will be described in detail with reference to Examples and Test Example, but the present invention is not limited thereto.

Example 1

Synthesis of bis-[2-(pivaloylamino)phenyl] disulfide (formula (I); R=t-butyl, X_1, X_2, X_3, X_4 =a hydrogen atom, Y=carbonyl, Z=2-(pivaloylamino)phenylthio)

[0111] Step 1) A mixture of bis-(2-aminophenyl) disulfide (8.00 g), pyridine (6.5 ml), and chloroform (150 ml) was stirred at 0°C, to which pivaloyl chloride (83 ml) was added dropwise. After completion of addition, the organic layer was washed with water and saturated brine. After drying the organic layer over anhydrous sodium sulfate and evapolation, solid material was obtained. The solid thus obtained was washed with ether-hexane and collected by filtration to give the desired compound (11.15 g, yield: 83%).

Example 2

Synthesis of bis-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl disulfide (formula (I); R=1-(2-ethylbutyl)cyclohexyl, X_1, X_2, X_3, X_4 =a hydrogen atom, Y=carbonyl, Z=2-(1-(2-ethylbutyl)cyclohexanecarbonylamino]phenylthio).

[0112]

i) A suspension of 60 % sodium hydride (980 mg) in tetrahydrofuran (80 ml) was stirred at room temperature and a tetrahydrofuran solution (10 ml) containing cyclohexanecarboxylic acid (3.00 g) was added dropwise thereto. After completion of addition, a mixture was stirred for 1 hour and cooled to 0°C, followed by adding a cyclohexane solution (18.7 ml) containing 1.5 M lithium isopropylamide dropwise thereto. Then, after stirring at room temperature for 1.5 hours and cooling to 0°C, a tetrahydrofuran solution (10 ml) containing 1-bromo-2-ethylbutane (4.64 g) was added dropwise thereto. The solution was gradually warmed to room temperature and stirred overnight. Water and a 10 % hydrochloride solution were added to this reaction solution and the solution was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After drying, the resulting solution was concentrated to obtain 1-(2-ethylbutyl)cyclohexanecarboxylic acid (3.17 g, yield: 64 %).
ii) A mixture of 1-(2-ethylbutyl)cyclohexane carboxylic acid (1.50 g) obtained in the above i), oxalyl chloride (0.85 ml), methylene chloride (20 ml), and a small amount of dimethylformamide was stirred at room temperature for 1 hour, concentrated under reduced pressure to obtain 1-(2-ethylbutyl)cyclohexanecarbonyl chloride as a crude product.

[0113] Step 1) A pyridine solution (20 ml) containing bis-(2-aminophenyl) disulfide (825 mg) was stirred at room temperature and a crude product of 1-(2-ethylbutyl)cyclohexanecarbonylchloride obtained in the above ii) was added dropwise thereto. After completion of addition, the solution was stirred overnight at 100°C. After concentration under

reduced pressure, water was added to the reaction solution and the solution was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate, followed by concentration. The resulting residue was purified by silica gel column chromatography (a developing solvent; hexane: ethyl acetate=15 : 1) to obtain the desired compound (667 mg, yield: 32 %).

Examples 3-8

[0114] The compounds shown in Tables 1 and 2 were obtained in the same manner as in Examples 1 and 2.

Table 1

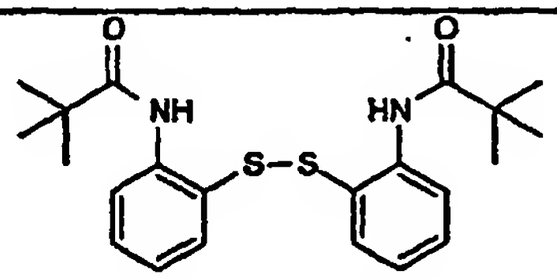
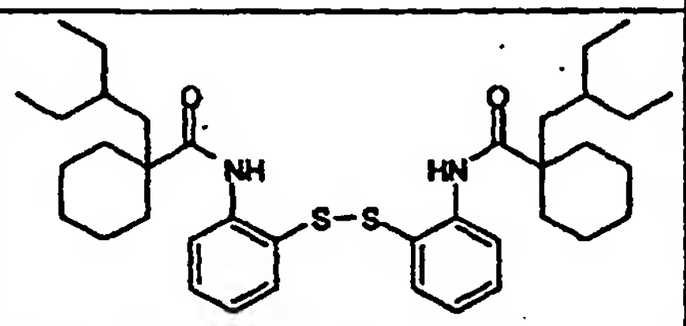
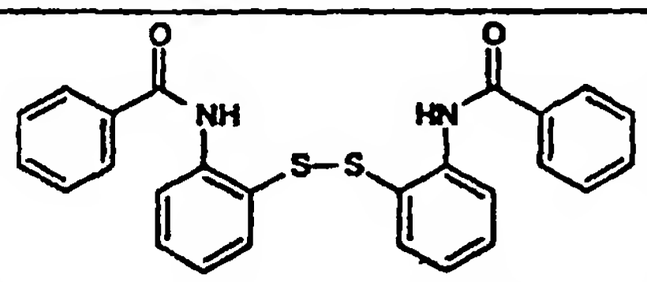
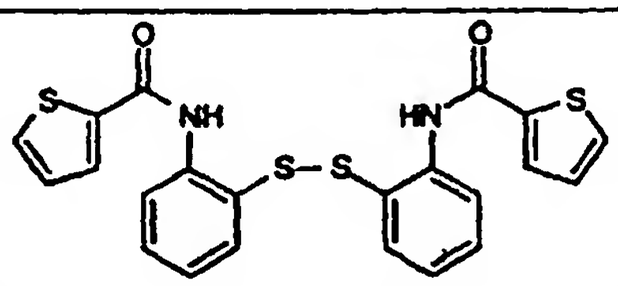
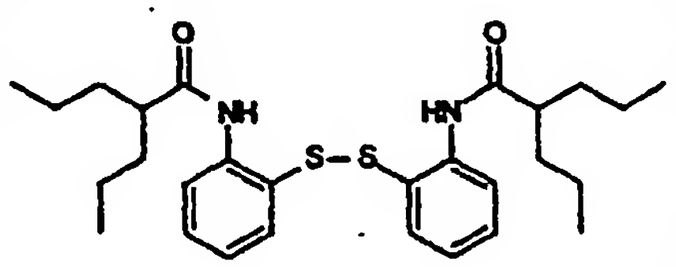
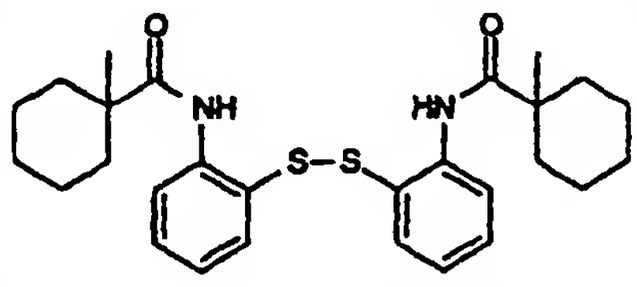
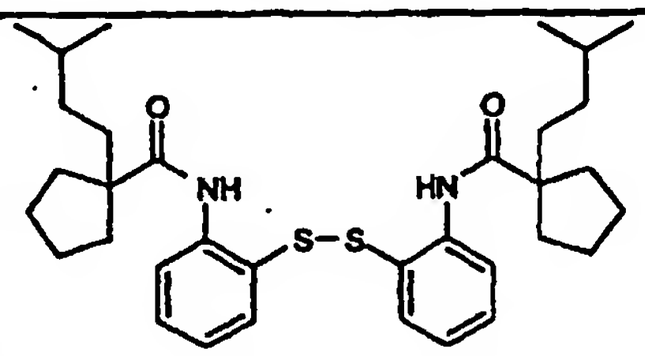
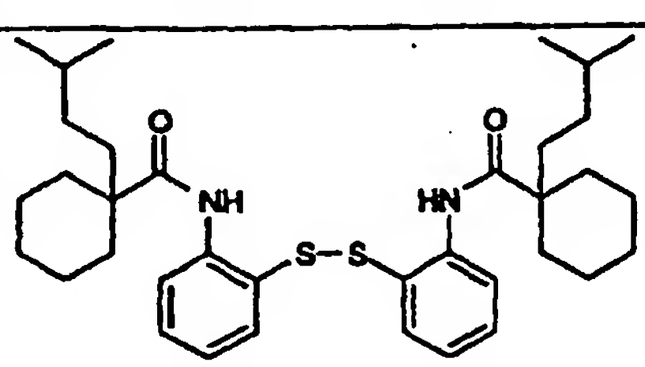
Example	Compound	m.p. (℃)	^{1}H NMR ($CDCl_3$ 300MHz)
1		86 - 87	8.52(2H, brs) 8.46(2H, dd, J=1.5, 8.4Hz) 7.40(2H, ddd, J=1.5, 7.8, 8.4Hz) 7.21(2H, dd, J=1.5, 7.8Hz) 6.94(2H, dt, J=1.5, 7.8Hz) 1.25(18H, s)
2		Amorphous	8.58(2H, brs) 8.48(2H, dd, J=1.5, 8.4Hz) 7.42(2H, ddd, J=1.5, 7.8, 8.4Hz) 7.13(2H, dd, J=1.5, 7.8Hz) 6.92(2H, dt, J=1.5, 7.8Hz) 1.90-2.10(4H, m) 1.10-1.80(30H, m) 0.78(12H, t, J=7.2Hz)
3		144 - 145	8.93(2H, brs) 8.50(2H, dd, J=1.5, 8.4Hz) 7.69(4H, dd, J=1.5, 8.4Hz) 7.40-7.60(8H, m) 7.31(2H, dt, J=1.5, 8.4Hz) 6.95(2H, dt, J=1.5, 7.8Hz)
4		156 - 157	8.78(2H, brs) 8.40(2H, dd, J=1.5, 8.4Hz) 7.55(2H, dd, J=1.2, 5.1Hz) 7.20-7.45(6H, m) 7.10(2H, dt, J=1.2, 5.1Hz) 6.95(2H, dt, J=1.5, 7.8Hz)
5		157 - 158	8.44(2H, dd, J=1.5, 8.4Hz) 8.04(2H, brs) 7.41(2H, ddd, J=1.5, 7.8, 8.4Hz) 7.24(2H, dd, J=1.5, 7.8Hz) 6.96(2H, dt, J=1.5, 7.8Hz) 2.05-2.20(2H, m) 1.20-1.70(16H, m) 0.93(12H, t, J=7.2Hz)
6		Amorphous	8.51(2H, brs) 8.48(2H, dd, J=1.5, 8.4Hz) 7.40(2H, ddd, J=1.5, 7.8, 8.4Hz) 7.22(2H, dd, J=1.5, 7.8Hz) 6.95(2H, dt, J=1.5, 7.8Hz) 1.80-2.00(4H, m) 1.25-1.70(16H, m) 1.18(6H, s)

Table 2

Example	Compound	m.p. (℃)	^{1}H NMR ($CDCl_3$ 300MHz)
7		Amorphous	8.46(2H, dd, J=1.5, 8.4Hz) 8.41(2H, brs) 7.40(2H, ddd, J=1.5, 7.8, 8.4Hz) 7.13(2H, dd, J=1.5, 7.8Hz) 6.91(2H, dt, J=1.5, 7.8Hz) 2.00-2.15(4H, m) 1.45-1.75(18H, m) 1.15-1.25(4H, m) 0.87(12H, d, J=6.6Hz)
8		Amorphous	8.50(2H, brs) 8.49(2H, dd, J=1.5, 8.4Hz) 7.41(2H, ddd, J=1.5, 7.8, 8.4Hz) 7.15(2H, dd, J=1.5, 7.8Hz) 6.92(2H, dt, J=1.5, 7.8Hz) 1.89-2.00(4H, m) 1.10-1.66(26H, m) 0.85(12H, d, J=6.6Hz)

[0115] The compounds 1-1 through 1-19 shown in Tables 3 and 4 were obtained in the same manner as in Examples 1 and 2.

Table 3

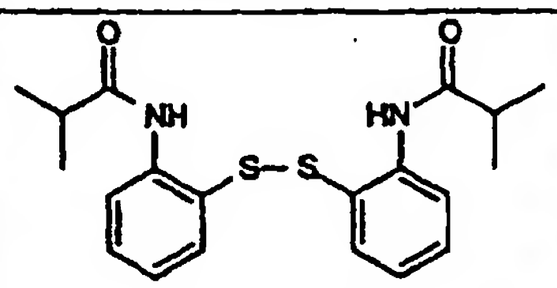
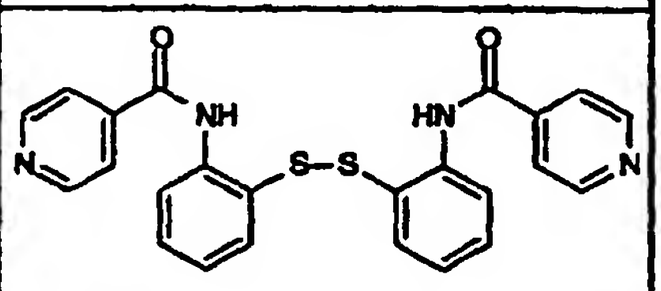
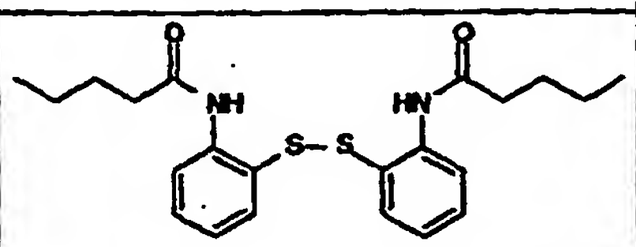
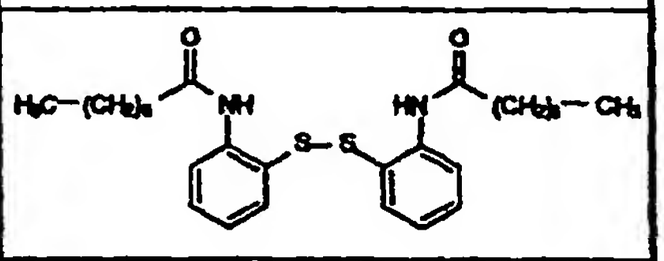
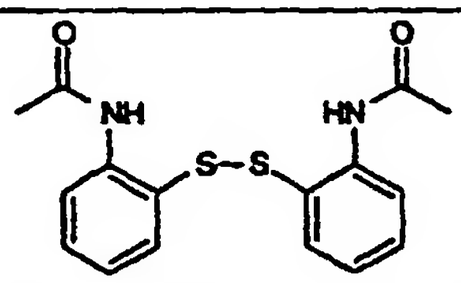
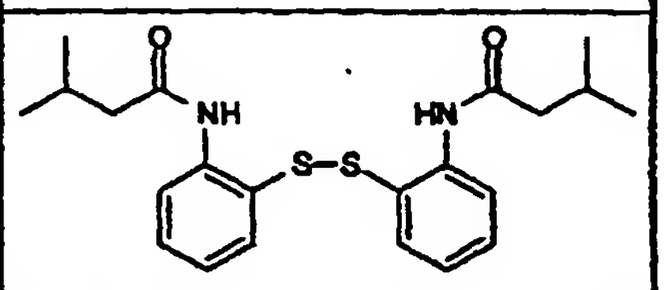
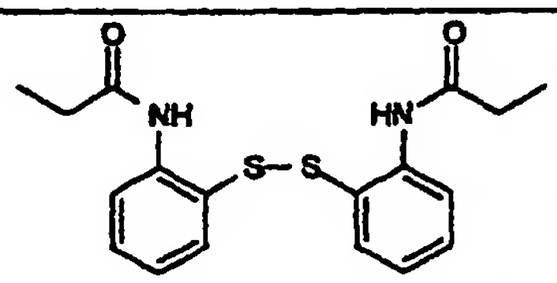
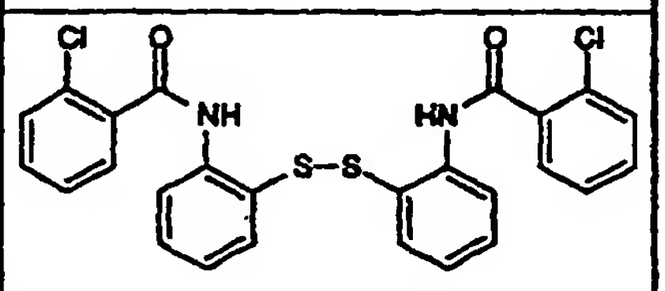
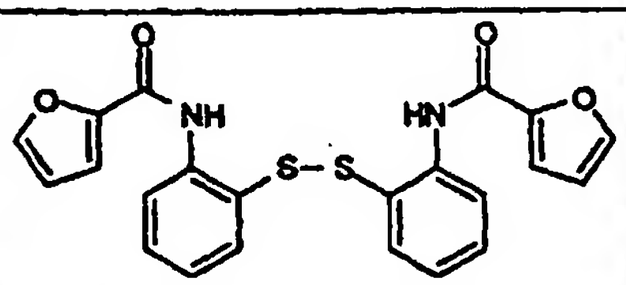
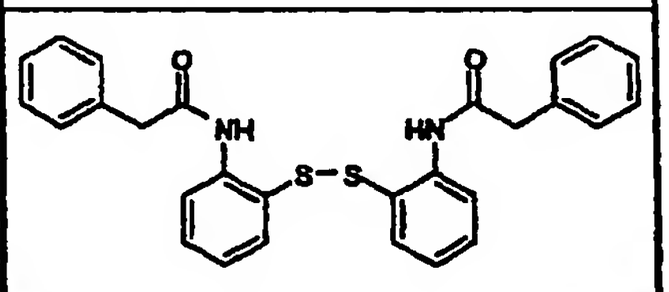
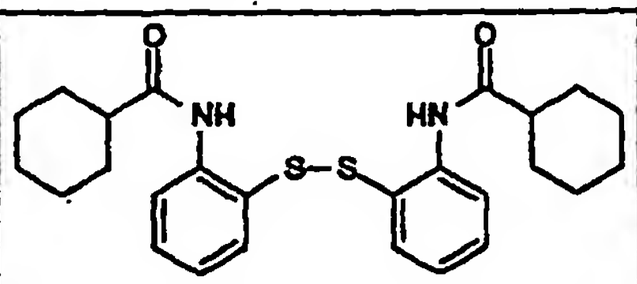
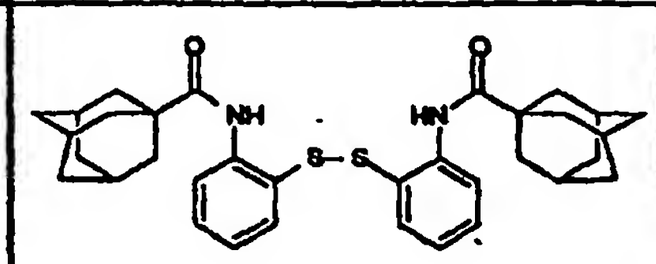
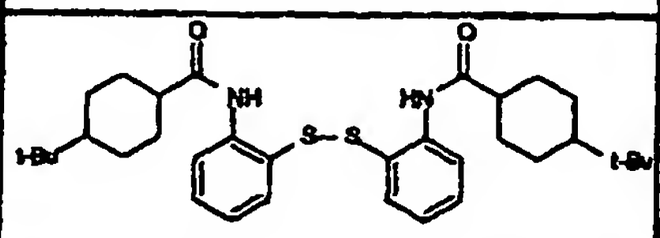
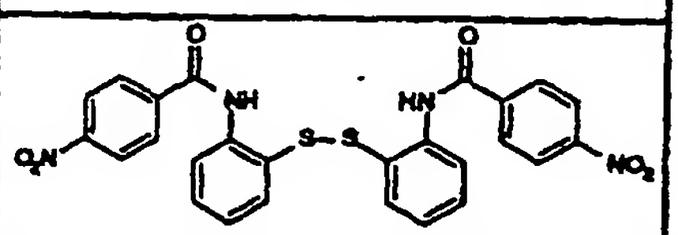
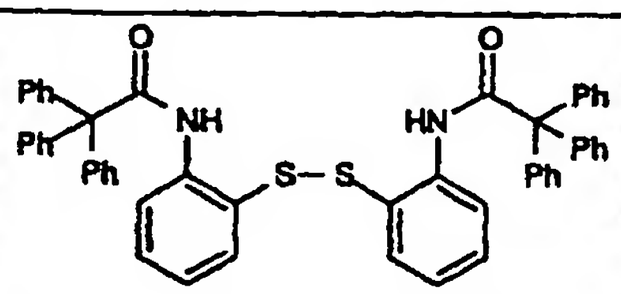
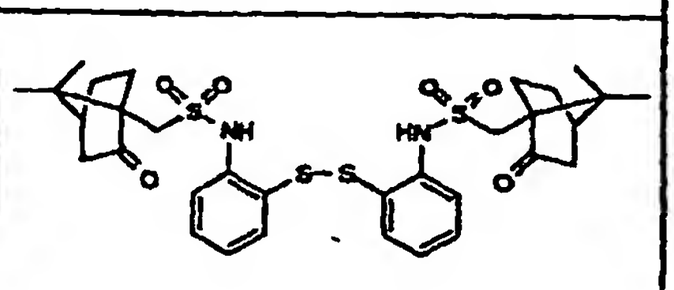
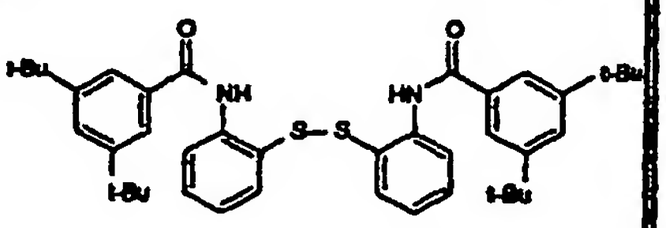
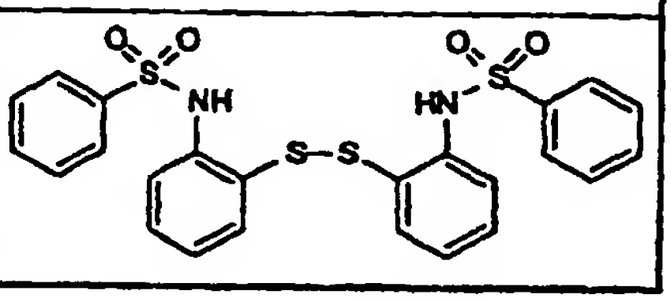
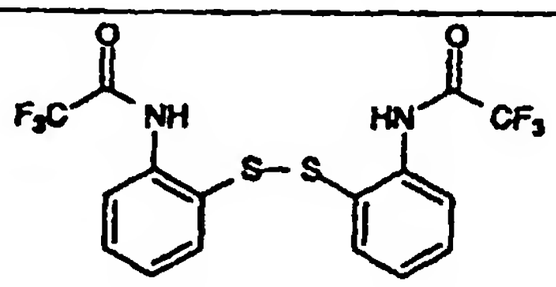
No.	Compound	No.	Compound
1-1		1-7	
1-2		1-8	
1-3		1-9	
1-4		1-10	
1-5		1-11	
1-6		1-12	

Table 4

No.	Compound	No.	Compound
1-13		1-17	
1-14		1-18	
1-15		1-19	
1-16			

Example 9

Synthesis of N-(2-mercaptophenyl)-2,2-dimethylpropioneamide (formula (I); R=t-butyl, X_1, X_2, X_3, X_4 =a hydrogen atom, Y=carbonyl, Z=a hydrogen atom).

[0116] Step 2) A mixture of bis-[2-(pivaloylamino)phenyl] disulfide (300 mg) obtained in Example 1 above in methanol (0.4 ml)-tetrahydrofuran (4 ml) was stirred at room temperature. Sodium borohydride (70 mg) was added thereto and the resulting solution was refluxed under heating for 4 hours. After cooling and addition of 10 % hydrochloric acid, the resulting solution was extracted with ethyl acetate. The organic layer was washed with water, and saturated brine, and was dried over anhydrous sodium sulfate. After drying, the solution was concentrated and the resulting residue was separated and purified by silica gel column chromatography (a developing solvent; hexane ; ethyl acetate=10:1) to obtain the desired compound (84 mg, yield: 28 %).

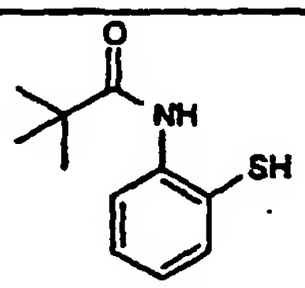
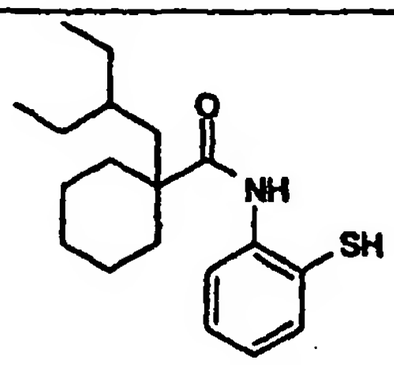
Example 10

Synthesis of N-(2-mercaptophenyl)-1-(2-ethylbutyl)cyclohexanecarboxamide (formula (I); R=1-(2-ethylbutyl)cyclohexyl, X_1, X_2, X_3, X_4 =a hydrogen atom, Y=carbonyl, Z=a hydrogen atom)

[0117] Step 2) A mixture of bis-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl] disulfide (667 mg) obtained in Example 2 above, triphenylphosphine (577 mg), dioxane (8 ml), and water (4 ml) was stirred for 1 hour at 50°C. After allowing the mixture to cool, a 1 N aqueous sodium hydroxide was added thereto. The aqueous layer was washed with hexane and neutralized with a 10 % hydrochloride solution. After extraction with ethyl acetate, the solution was washed with saturated brine and dried over anhydrous sodium sulfate. After drying, the solution was concentrated and the thus-

obtained residue was purified by silica gel column chromatography (a developing solvent; hexane : ethyl acetate=15:1), which resulted in the desired compound (378mg, yield: 56 %).

Table 5

Example	Compound	m.p. (℃)	^{1}H NMR ($CDCl_3$ 300MHz)
9		69- 71	8.42(1H, brs) 8.31(1H, dd, J=1.5, 8.4Hz) 7.50(1H, dd, J=1.5, 7.8Hz) 7.30(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.00(1H, dt, J=1.5, 7.8Hz) 3.08(1H, s) 1.36(9H, s)
10		68.5 - 74.0	8.45(1H, brs) 8.33(1H, dd, J=1.5, 8.4Hz) 7.51(1H, dd, J=1.5, 7.8Hz) 7.31(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.00(1H, dt, J=1.5, 7.8Hz) 3.07(1H, s) 2.05-2.25(2H, m) 1.20-1.80(15H, m) 0.79(6H, t, J=6.9Hz)

Example 11

Synthesis of N-(2-mercaptophenyl)-1-isopentylcyclohexanecarboxamide (formula (I); R=1-isopentylcyclohexyl, X_1, X_2, X_3, X_4 =a hydrogen atom, Y=carbonyl, Z=a hydrogen atom).

Step 6) N-[2-(1-isopentylcyclohexane)carbonylthiophenyl]-1-isopentylcyclohexanecarboxamide (formula (XI); R=1-isopentyl-cyclohexyl, X_1, X_2, X_3, X_4 =a hydrogen atom, Y=carbonyl)

[0118] A pyridine solution (500 ml) containing 2-aminothiophenol (15.8 g) was stirred at room temperature and 2 equal volumes of 1-isopentylcyclohexanecarbonyl chloride was added dropwise thereto. After completion of addition, the solution was stirred for 2 hours at 60°C and allowed to cool. After removal of pyridine under reduced pressure, water was added and the solution was extracted with ethyl acetate. The organic layer was washed with an aqueous solution of saturated sodium bicarbonate, hydrochloric acid, and saturated brine, in this order, and dried over anhydrous sodium sulfate. The resulting solution was concentrated under reduced pressure to give the desired compound in the form of a crude oily substance (60 g).

[0119] Step 7) The crude product obtained in the above step 6) (60 g) was dissolved in a mixed solvent of methanol (60 ml)-tetrahydrofuran (60 ml) in the atmosphere of argon. Potassium hydroxide (24.2 g) was added thereto and the solution was stirred for 1 hour at room temperature. After stirring, water (50 ml) was added, the solution was washed with hexane (50 ml x 3), and the aqueous layer was acidified with potassium hydrogen sulfate, followed by extraction with chloroform. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and the solvent was removed by evapolation under reduced pressure. The resulting deposited crystalline product was washed with pentane and collected by filtration to obtain the desired compound (23.1 g, yield: 60 %).

Examples 12-18

[0120] The compounds shown in Tables 6 and 7 were obtained in the same manner as in Example 11.

Table 6

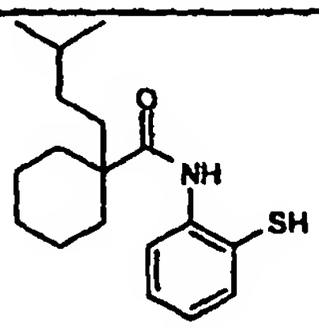
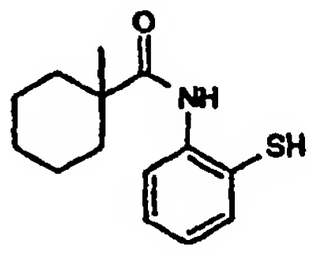
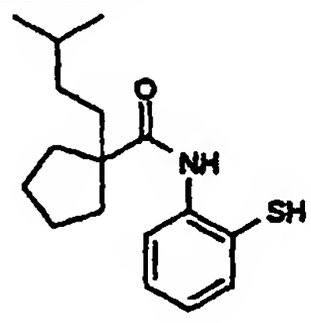
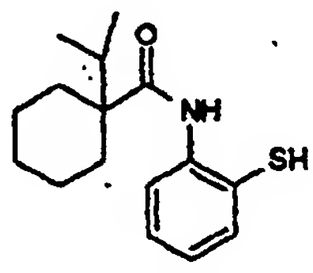
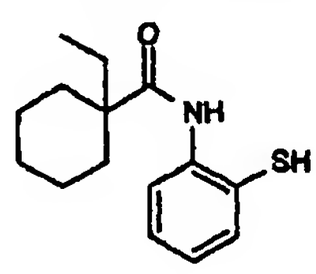
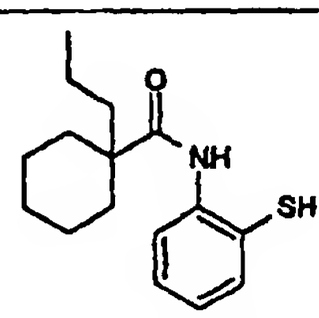
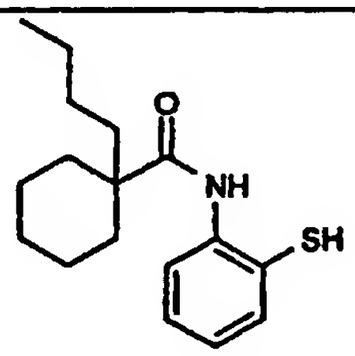
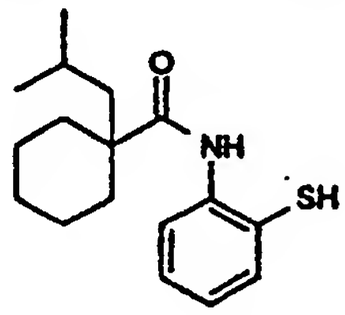
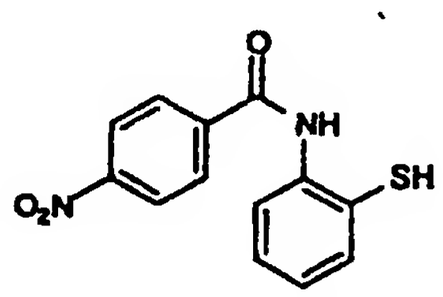
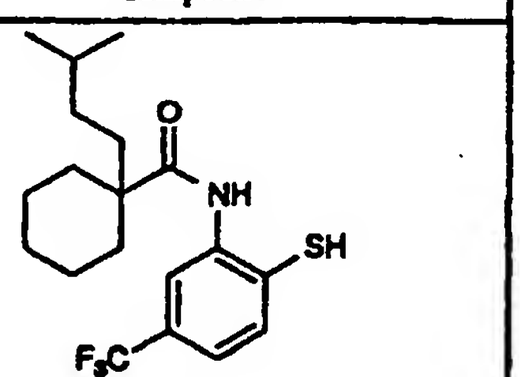
Example	Compound	m.p. (℃)	^{1}H NMR ($CDCl_3$ 300MHz)
11		109 - 110	8.34(1H, brs) 8.30(1H, dd, J=1.5, 8.4Hz) 7.50(1H, dd, J=1.5, 7.8Hz) 7.31(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.00(1H, dt, J=1.5, 7.8Hz) 3.01(1H, s) 1.10-2.20(15H, m) 0.85(6H, d, J=6.6Hz)
12		82 - 83	8.42(1H, brs) 8.31(1H, dd, J=1.5, 8.4Hz) 7.50(1H, dd, J=1.5, 7.8Hz) 7.31(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.00(1H, dt, J=1.5, 7.8Hz) 3.07(1H, s) 2.04-2.20(2H, m) 1.25-1.75(8H, m) 1.30(3H, s)
13		66 - 68	8.27(1H, dd, J=1.5, 8.4Hz) 8.26(1H, brs) 7.50(1H, dd, J=1.5, 7.8Hz) 7.30(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.00(1H, dt, J=1.5, 7.8Hz) 3.06(1H, s) 2.15-2.30(2H, m) 1.40-1.80(9H, m) 1.15(2H, m) 0.85(6H, d, J=6.6Hz)
14		120 - 121	8.37(1H, brs) 8.35(1H, dd, J=1.5, 8.4Hz) 7.50(1H, dd, J=1.5, 7.8Hz) 7.31(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.00(1H, dt, J=1.5, 7.8Hz) 3.07(1H, s) 2.12-2.20(2H, m) 1.15-1.83(9H, m) 0.97(6H, d, J=6.9Hz)
15		84 - 85	8.38(1H, brs) 8.32(1H, dd, J=1.5, 8.4Hz) 7.50(1H, dd, J=1.5, 7.8Hz) 7.31(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.00(1H, dt, J=1.5, 7.8Hz) 3.07(1H, s) 2.05-2.19(2H, m) 1.20-1.70(10H, m) 0.90(3H, t, J=7.2Hz)
16		93 - 94	8.38(1H, brs) 8.32(1H, dd, J=1.5, 8.4Hz) 7.50(1H, dd, J=1.5, 7.8Hz) 7.30(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.00(1H, dt, J=1.5, 7.8Hz) 3.07(1H, s) 2.05-2.20(2H, m) 1.20-1.70(12H, m) 0.88(3H, t, J=7.2Hz)

Table 7

Example	Compound	m.p. (℃)	^{1}H NMR ($CDCl_3$ 300MHz)
17		97 - 98	8.37(1H, brs) 8.31(1H, dd, J=1.5, 8.4Hz) 7.50(1H, dd, J=1.5, 7.8Hz) 7.30(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.00(1H, dt, J=1.5, 7.8Hz) 3.07(1H, s) 2.05-2.20(2H, m) 1.20-1.70(14H, m) 0.87(3H, t, J=7.2Hz)
18		92 - 93	8.42(1H, brs) 8.32(1H, dd, J=1.5, 8.4Hz) 7.51(1H, dd, J=1.5, 7.8Hz) 7.31(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.00(1H, dt, J=1.5, 7.8Hz) 3.07(1H, s) 2.06-2.20(2H, m) 1.20-1.95(11H, m) 0.89(6H, d, J=6.6Hz)

[0121] Further, the compounds 11-1 and 11-2 shown in Table 8 were obtained in the same manner as in Example 11.

Table 8

No.	Compound	No.	Compound
11-1		11-2	

Example 19

Synthesis of N-(2-mercapto-5-methoxyphenyl)-1-methylcyclohexanecarboxamide (formula (I); R=1-methylcyclohexyl, X_1, X_3, X_4 =a hydrogen atom, X_2=methoxy, Y=carbonyl, Z=a hydrogen atom

Step 8) S-(4-methoxy-2-nitrophenyl) N,N-dimethylthiocarbamate (formula (VIII); R_{11}, R_{12} methyl, X_1, X_3, X_4 =a hydrogen atom, X_2=methoxy).

[0122] A dimethylformamide solution (20 ml) containing 4-methoxy-2-nitrophenol (4.00 g) was added dropwise to a suspension of sodium hydride (1.04 g) in dimethylformamide (40 ml) at 0°C under stirring. After completion of addition, the mixture was stirred for 30 minutes at room temperature, dimethylthiocarbamoyl chloride (3.65 g) was further added thereto and the solution was stirred for 1 hour at 80°C. After allowing the solution to cool, water was added thereto and

the solution was extracted with ethyl acetate. The organic layer was washed with 5 % hydrochloric acid, water, and saturated brine, and was dried over anhydrous sodium sulfate. The solution was concentrated and ether-hexane was added to the residue thus obtained. A deposited solid was collected by filtration to obtain a yellow solid (5.11 g, yield: 84 %). Then, phenyl ether (10 ml) was added to the resulting product (3.50 g). After stirring for 1 hour at 210°C, the solution was allowed to cool. The resulting solution was purified by silica gel column chromatography (a developing solvent; hexane : ethyl acetate=7:1-3:2) to obtain the desired compound (3.35 g, yield: 96 %).

Step 9) S-[2-(1-methylcyclohexanecarbonylamino)-4-methoxyphenyl) N,N-dimethylthiocarbamate (formula (IX); R=1-methylcyclohexyl, R_{11}, R_{12}=methyl, X_1, X_3, X_4=a hydrogen atom, X_3 =methoxy, Y=carbonyl)

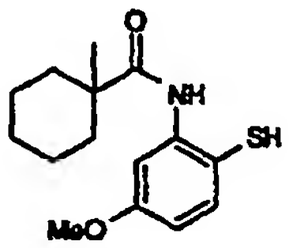
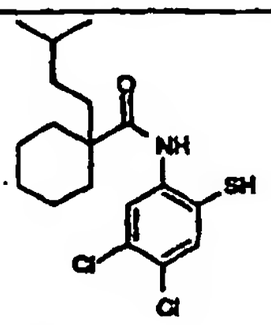
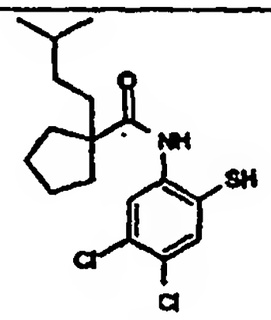
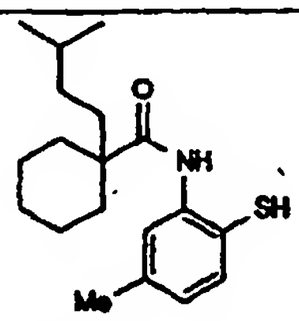
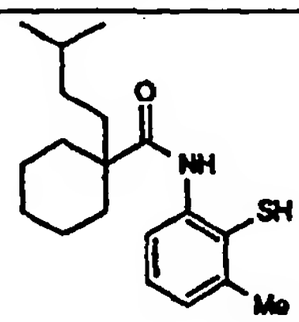
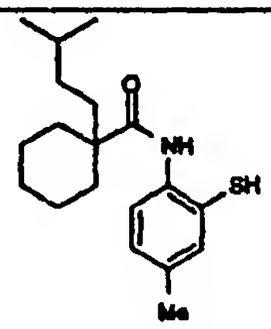
[0123] An ethyl acetate solution (75 ml) containing the compound (2.00 g) obtained in the above step 8) and $SnCl_2 \cdot 2H_20$ (3.65 g) was stirred at room temperature overnight. Ethyl acetate (100 ml) was added to the solution and, then, an aqueous sodium hydroxide was further added thereto. Magnesium sulfate was added to the mixture and solid deposited was filtered off. The filtrate was concentrated to obtain S-(2-amino-4-methoxyphenyl) N,N-dimethylthiocarbamate (1.64 g, yield: 93 %). After addition of pyridine (2.9 ml) and chloroform (20 ml) thereto, 1-methylcyclohexanecarbonyl chloride (1.39 g) was added dropwise thereto at room temperature under stirring, followed by stirring for 1 hour. After distilling off the solvent, water was added and the solution was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and was dried over anhydrous sodium sulfate. The residue obtained by concentration was purified by silica gel column chromatography (a developing solvent; hexane : ethyl acetate=3:1) to obtain the desired compound (2.41 g, yield: 95 %).

[0124] Step 10) The compound obtained in the above step 9) (250 mg) was added to a solution containing potassium hydroxide (140 mg) and methanol (1.5 ml)-tetrahydrofuran (0.5 ml), and the mixture was refluxed for 30 minutes under heating. After allowing to cool, water was added and the aqueous layer was washed with hexane. The solution was acidified by adding an aqueous potassium hydrogensulfate, followed by extraction with ethyl acetate. The organic layer was washed with water and a saturated brine, and was dried over anhydrous sodium sulfate. The residue obtained after concentration was purified by column chromatography (a developing solvent; hexane:ethyl acetate = 40:1) to obtain the desired compound (104 mg, yield: 52 %).

Examples 20-24

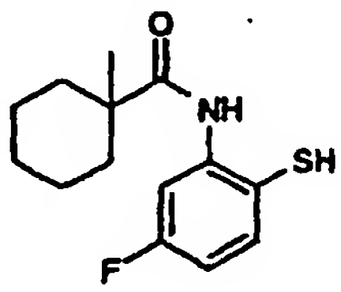
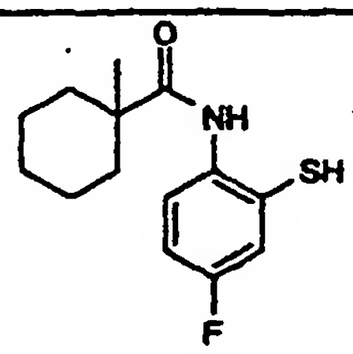
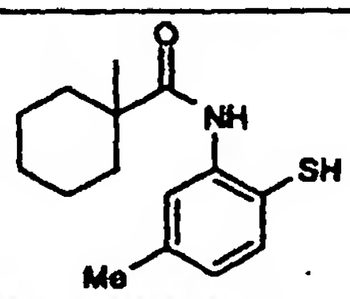
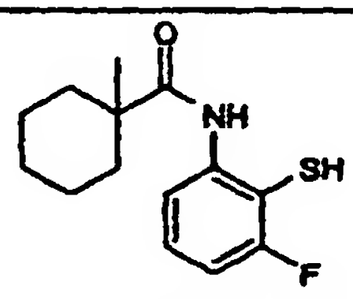
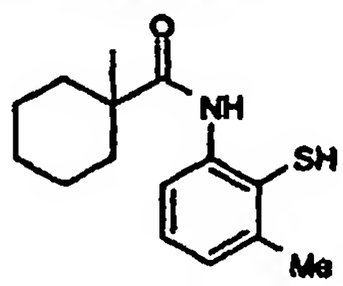
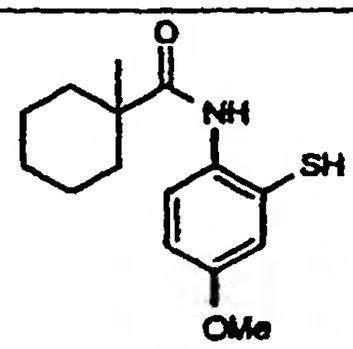
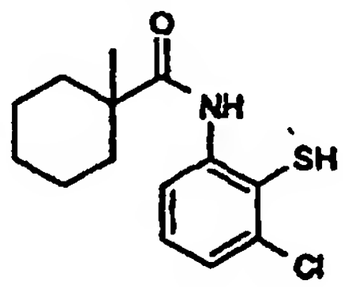
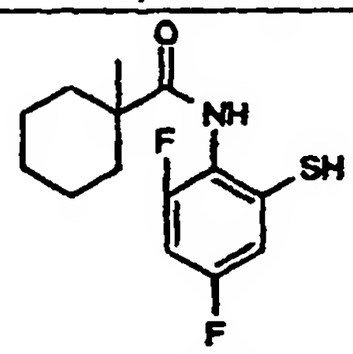
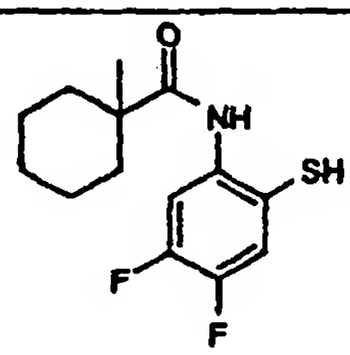
[0125] The compounds shown in Table 9 were obtained in the same manner as in Example 19.

Table 9

Example	Compound	m.p. (℃)	^{1}H NMR ($CDCl_3$ 300MHz)
19		Oil	8.75(1H, brs) 8.19(1H, d, J=2.7Hz) 7.42(1H, d, J=8.4Hz) 6.57(1H, dd, J=2.7, 8.4Hz) 3.82(3H, s) 2.91(1H, s) 2.05-2.15(2H, m) 1.25-1.70(8H, m) 1.30(3H, s)
20		103 - 107	8.59(1H, s) 8.34(1H, brs) 7.61(1H, s) 3.10(1H, s) 2.00-2.20(2H, m) 1.10-1.75(13H, m) 0.86(6H, d, J=6.6Hz)
21		56 - 57	8.75(1H, s) 8.55(1H, brs) 7.60(1H, s) 3.09(1H, s) 1.10-2.20(13H, m) 0.87(6H, d, J=6.6Hz)
22		83.5 - 85.5	8.44(1H, brs) 8.22(1H, d, J=1.5Hz) 7.33(1H, d, J=7.8Hz) 6.83(1H, dd, J=1.5, 7.8Hz) 2.96(1H, s) 2.34(3H, s) 1.10-2.20(15H, m) 0.85(6H, d, J=6.6Hz)
23		85 - 87	8.50(1H, brs) 8.17(1H, dd, J=1.5, 8.4Hz) 7.21(1H, t, J=8.4Hz) 7.00(1H, dd, J=1.5, 8.4Hz) 2.73(1H, brs) 2.47(3H, s) 2.05-2.20(2H, m) 1.10-1.75(13H, m) 0.86(6H, d, J=6.6Hz)
24		71-72	8.20(1H, brs) 8.12(1H, d, J=8.4Hz) 7.31(1H, s) 7.10(1H, d, J=8.4Hz) 3.05(1H, s) 2.28(3H, s) 2.08-2.16(2H, m) 1.13-1.60(13H, m) 0.85(6H, d, J=6.6Hz)

[0126] The compounds 19-1 through 19-9 shown in Table 10 were also obtained in the same manner as in Example 19.

Table 10

No.	Compound	No.	Compound
19-1		19-6	
19-2		19-7	
19-3		19-8	
19-4		19-9	
19-5			

Example 25

Synthesis of S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] thioacetate (formula (I); R=1-isopentylcyclohexyl, X_1, X_2, X_3, X_4=a hydrogen atom, Y=carbonyl, Z=acetyl)

[0127] Step 4) Acetyl chloride (0.17 ml) was added dropwise to a chloroform solution (10 ml) containing N-(2-mercaptophenyl)-1-isopentylcyclohexanecarboxamide (600 mg) obtained in the same manner as in step 2) of Example 9, step 7) of Example 11, or the step 10) of Example 19 and pyridine (0.48 ml) at room temperature under stirring. The solution was stirred for 1 hour. The residue obtained after concentration was purified by silica gel column chromatography (a developing solvent; hexane : ethyl acetate=12:1) to obtain the desired compound (666 mg, yield: 98 %).

Example 26

Synthesis of S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]-phenyl] 2-methylthiopropionate (formula (I); R=1-(2-ethylbutyl)cyclohexyl, X_1, X_2, X_3, X_4 =a hydrogen atom, Y=carbonyl, Z=isobutyryl)

[0128] Step 4) Isobutyryl chloride (15.0 ml) was added dropwise to a chloroform solution (300 ml) containing N-(2-mercaptophenyl)-1-(2-ethylbutyl)cyclohexanecarboxamide (43.72 g) obtained in Example 10 and pyridine (27.7 ml) at room temperature under stirring. The solution was stirred for 1 hour. After concentration, hexane was added and the deposited solid was filtered off. The filtrate was concentrated and the resulting residue was purified by silica gel column chromatography (a developing solvent; hexane : ethyl acetate=15:1) to obtain the desired compound (50.72 g, yield: 95%).

Example 27

Synthesis of S-[2-(1-isobutylcyclohexanecarbonylamino)phenyl] 2-methylthiopropionate (formula (I); R=1-isobutylcyclohexyl, X_1, X_2, X_3, X_4=a hydrogen atom, Y=carbonyl, Z=isobutyryl)

[0129] Step 4) Isobutyryl chloride (0.92 ml) was added dropwise to a chloroform solution (25 ml) containing N-(2-mercaptophenyl)-1-isobutylcyclohexanecarboxamide (2.50 g) obtained in Example 18 and pyridine (1.8 ml) at room temperature under stirring. The solution was stirred for 1 hour. The residue obtained after concentration was purified by silica gel column chromatography (a developing solvent; hexane : ethyl acetate=15:1) to obtain the desired compound (2.94 g, yield: 95%).

Example 28

Synthesis of S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino)-phenyl] 1-acetylpiperidine-4-thiocarboxylate (formula (I); R=1-(2-ethylbutyl)cyclohexyl, X_1, X_2, X_3, X_4=a hydrogen atom, Y=carbonyl, Z=1-acetyl-4-piperidinecarbonyl)

[0130] Step 4) A chloroform solution (10 ml) containing N-(2-mercaptophenyl)-1-(2-ethylbutyl)cyclohexanecarboxamide (933 mg) obtained in Example 10 and pyridine (0.5 ml)was added dropwise to a chloroform solution (10 ml) containing 1-acetylisonipecotic acid (500 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (616 mg), and 1-hydroxybenzotriazole (435 mg) at room temperature. The solution was stirred for 1 hour. After stirring, water was added and the solution was extracted with ethyl acetate. The organic layer was washed with a saturated brine and dried over anhydrous sodium sulfate. The residue obtained after concentration was purified by silica gel column chromatography (a developing solvent; hexane : ethyl acetate=4:1-chloroform : methanol=10:1) to obtain the desired compound (1.08 g, yield: 79 %).

Example 28'

[0131] The compound of Example 28 (formula (I); R=1-(2-ethylbutyl)-cyclohexyl, X_1, X_2, X_3, X_4=a hydrogen atom, Y=carbonyl, Z=1-acetyl-4-piperidinecarbonyl) was synthesized using another synthesis method.

[0132] Step 4) Triethylamine (541 ml) was added to an ethylacetate suspension (2 liters) containing 1-acetylisonipecotic acid (331 g) under a stream of argon. The solution was stirred under ice cooling. An ethyl acetate solution (400 ml) containing ethyl chlorocarbonate (185 ml) was added dropwise thereto and the mixture was further stirred for 100 min under spontaneous elevation of the temperature. After ice-cooling, an ethyl acetate solution (2 liters) of N-(2-mercaptophenyl)-1-(2-ethylbutyl)cyclohexanecarboxamide (618 g) obtained in Example 10 was added dropwise to the reaction solution, which was stirred further for 15 minutes under ice-cooling. After stirring, 1 N hydrochloric acid (1.3 liter) was added, the organic layer was washed successively with water, an aqueous saturated sodium bicarbonate, water, and a saturated brine, and dried over anhydrous sodium sulfate. The residue obtained after concentration was dissolved in diisopropyl ether (2.5 liter) and the solution was stirred for crystallization to obtain a crude crystal. The crystal was further dissolved in diisopropyl ether (5.5 liter) under heating and the solution was stirred for crystallization to obtain the desired compound (505 g, yield:55 %).

Examples 29-65

[0133] The compounds shown in Tables 11-17 were obtained in the same manner as in Examples 25, 26, 27, 28, or 28'.

Table 11

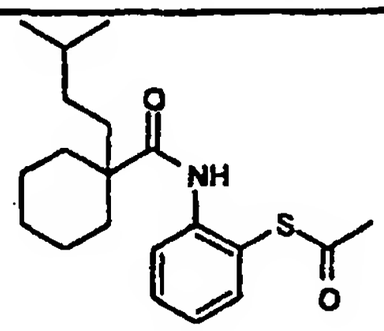
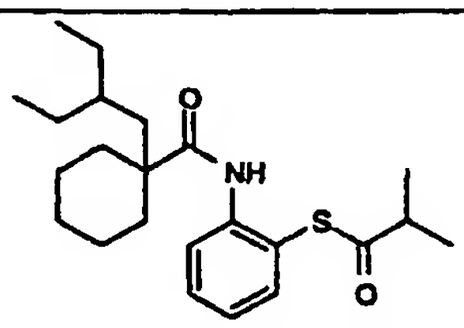
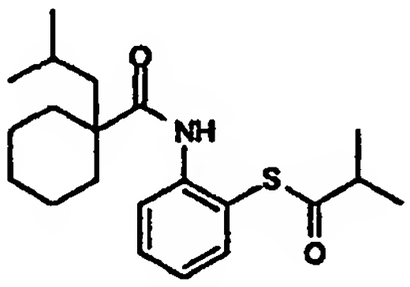
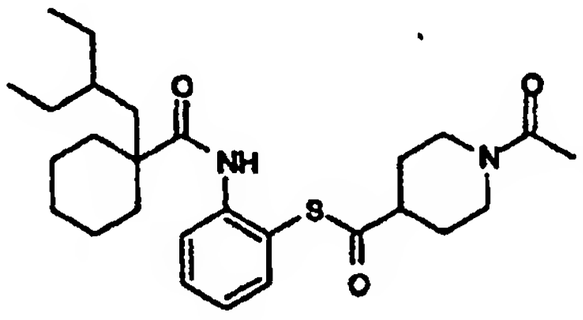
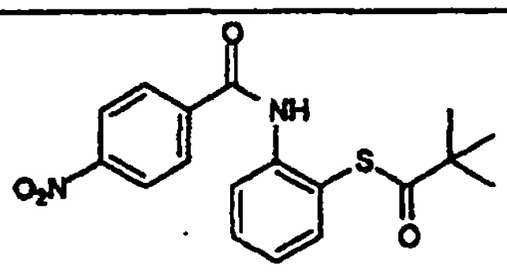
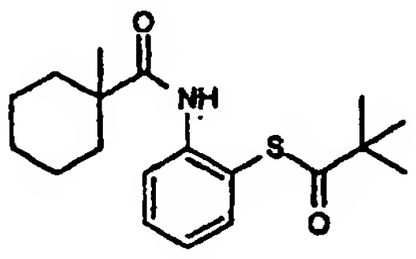
Example	Compound	m.p. (℃)	^{1}H NMR ($CDCl_3$ 300MHz)
25		54 - 55	8.34(1H, dd, J=1.5, 8.4Hz) 8.05(1H, brs) 7.46(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.39(1H, dd, J=1.5, 7.8Hz) 7.12(1H, dt, J=1.5, 7.8Hz) 2.45(3H, s) 2.03(2H, m) 1.10-1.61(13H, m) 0.85(6H, d, J=6.6Hz)
26		63.0 -63.5	8.40(1H, dd, J=1.5, 8.4Hz) 8.12(1H, brs) 7.45(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.38(1H, dd, J=1.5, 7.8Hz) 7.11(1H, dt, J=1.5, 7.8Hz) 2.94(2H, sept, J=6.9Hz) 1.95-2.20(2H, m) 1.15-1.75(15H, m) 1.30(6H, d, J=6.9Hz) 0.78(6H, t, J=6.9Hz)
27		63.5 - 65.5	8.39(1H, dd, J=1.5, 8.4Hz) 8.10(1H, brs) 7.45(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.38(1H, dd, J=1.5, 7.8Hz) 7.11(1H, dt, J=1.5, 7.8Hz) 2.94(2H, sept, J=6.9Hz) 1.95-2.10(2H, m) 1.10-1.85(11H, m) 1.29(6H, d, J=6.9Hz) 0.87(6H, d, J=6.6Hz)
28		89.0 -.91.5	8.37(1H, dd, J=1.5, 8.4Hz) 8.03(1H, brs) 7.46(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.36(1H, dd, J=1.5, 7.8Hz) 7.11(1H, dt, J=1.5, 7.8Hz) 4.58(1H, m) 3.88(1H, m) 3.18(1H, m) 2.91(1H, m) 2.82(1H, m) 1.95-2.20(4H, m) 2.11(3H, s) 1.15-1.85(17H, m) 0.78(6H, t, J=6.9Hz)
29		144 - 145	8.52(1H, brs) 8.42(1H, dd, J=1.5, 8.1Hz) 8.34(2H, dd, J=1.8, 6.9Hz) 8.00(2H, dd, J=1.8, 6.9Hz) 7.54(1H, ddd, J=1.5, 7.5, 8.1Hz) 7.45(1H, dd, J=1.5, 7.5Hz) 7.23(1H, dt, J=1.5, 7.5Hz) 1.34(9H, s)
30		41 - 42	8.39(1H, dd, J=1.5, 8.4Hz) 8.07(1H, brs) 7.44(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.36(1H, dd, J=1.5, 7.8Hz) 7.10(1H, dt, J=1.5, 7.8Hz) 1.96-2.05(2H, m) 1.15-1.65(8H, m) 1.35(9H, s) 1.22(3H, s)

Table 12

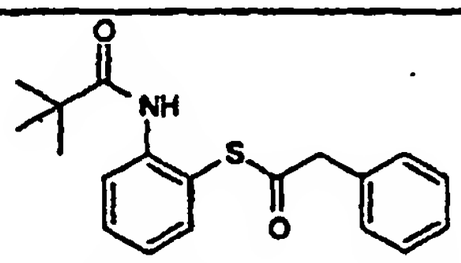
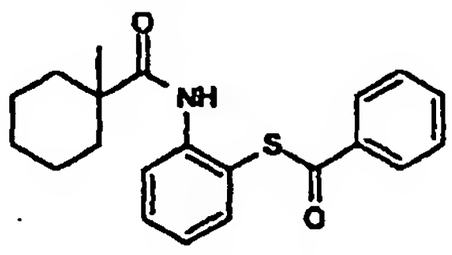
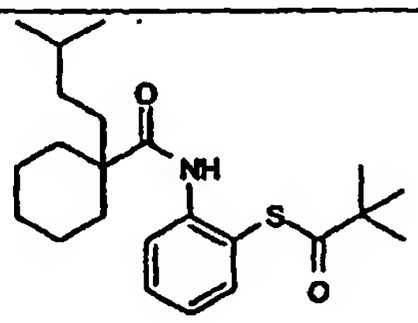
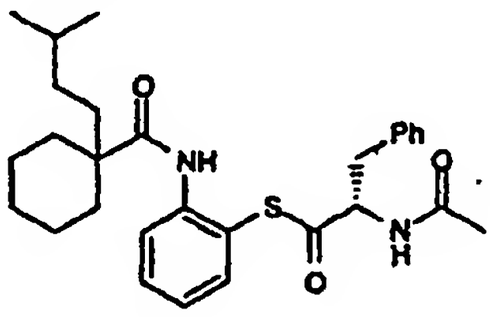
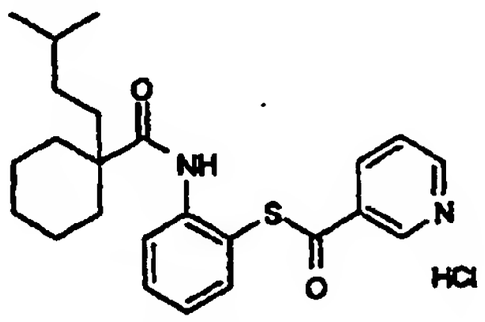
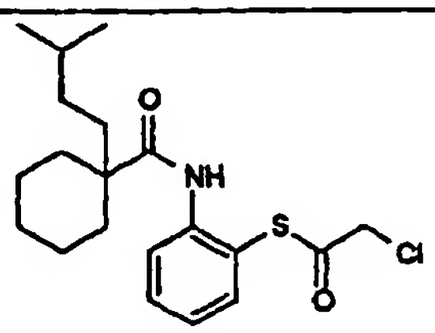
Example	Compound	m.p. (℃)	^{1}H NMR ($CDCl_3$ 300MHz)
3 1		61 - 62	8.32(1H, dd, J=1.5, 8.4Hz) 7.85(1H, brs) 7.20-7.50(7H, m) 7.10(1H, dt, J=1.5, 7.8Hz) 3.94(2H, s) 1.17(9H, s)
3 2		78.5 - 79.0	8.40(1H, dd, J=1.5, 8.4Hz) 8.17(1H, brs) 8.05(2H, m) 7.66(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.43-7.60(4H, m) 7.17(1H, dt, J=1.5, 7.8Hz) 1.85-2.00(2H, m) 1.10-1.70(8H, m) 1.18(3H, s)
3 3		55 - 56	8.39(1H, dd, J=1.5, 8.4Hz) 8.04(1H, brs) 7.45(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.36(1H, dd, J=1.5, 7.8Hz) 7.10(1H, dt, J=1.5, 7.8Hz) 2.00-2.03(2H, m) 1.10-1.60(13H, m) 1.35(9H, s) 0.85(6H, d, J=6.6Hz)
3 4		155 - 156	8.39(1H, dd, J=1.5, 8.4Hz) 7.98(1H, brs) 7.47(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.09-7.38(7H, m) 5.85(1H, d, J=7.8Hz) 5.04(1H, dt, J=5.7, 7.8Hz) 3.20(1H, dd, J=6.0, 14.1Hz) 3.11(1H, dd, J=7.5, 14.1Hz) 1.97-2.10(5H, m) 1.00-1.80(13H, m) 0.81(6H, d, J=6.6Hz)
3 5		106 - 110	9.42(1H, s) 9.14(1H, d, J=5.1Hz) 8.90(1H, d, J=8.1Hz) 8.32(1H, d, J=7.8Hz) 8.12(1H, m) 7.89(1H, s) 7.58(1H, t, J=7.8Hz) 7.49(1H, d, J=7.8Hz) 7.24(1H, t, J=7.8Hz) 5.94(1H, brs) 1.89- 2.03(2H, m) 1.07-1.60(13H, m) 0.80(6H, d, J=6.6Hz)
3 6		68 - 69	8.35(1H, dd, J=1.5, 8.4Hz) 7.93(1H, brs) 7.50(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.40(1H, dd, J=1.5, 7.8Hz) 7.15(1H, dt, J=1.5, 7.8Hz) 4.28(2H, s) 1.96-2.09(2H, m) 1.09-1.65(13H, m) 0.85(6H, d, J=6.6Hz)

Table 13

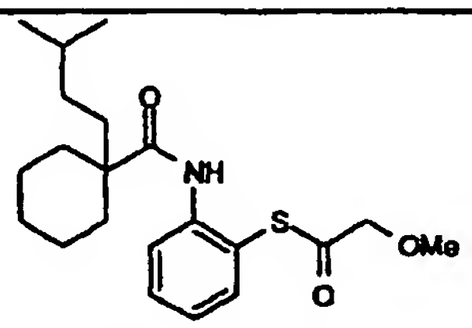
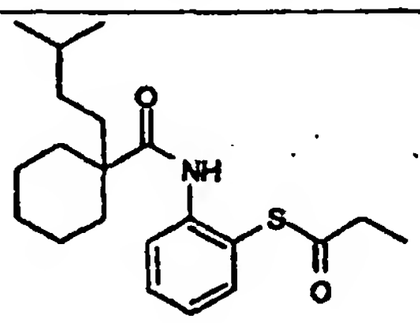
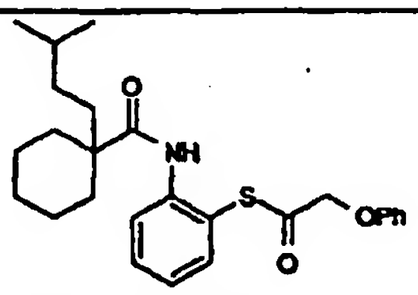
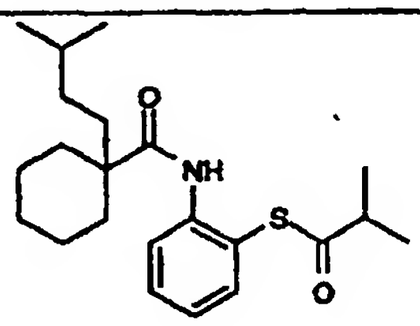
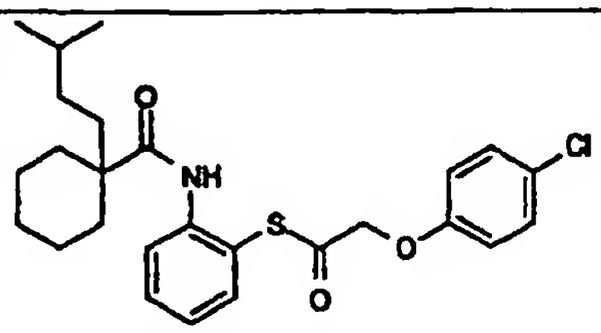
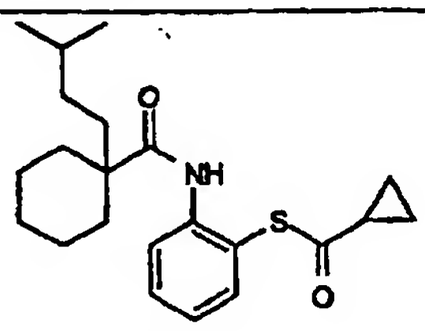
Example	Compound	m.p. (℃)	^{1}H NMR ($CDCl_3$ 300MHz)
37		53 - 54	8.37(1H, dd, J=1.5, 8.4Hz) 7.98(1H, brs) 7.47(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.39(1H, dd, J=1.5, 7.8Hz) 7.13(1H, dt, J=1.5, 7.8Hz) 4.19(2H, s) 3.58(3H, s) 1.95-2.10(2H, m) 1.05-1.65(13H, m) 0.84(6H, d, J=6.6Hz)
38		40 - 41	8.35(1H, dd, J=1.5, 8.4Hz) 8.06(1H, brs) 7.45(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.39(1H, dd, J=1.5, 7.8Hz) 7.17(1H, dt, J=1.5, 7.8Hz) 2.72(2H, q, J=7.5Hz) 1.95-2.10(2H, m) 1.10-1.60(13H, m) 1.24(3H, t, J=7.2Hz) 0.85(6H, d, J=6.6Hz)
39		60.5 - 62.0	8.37(1H, dd, J=1.5, 8.4Hz) 7.90(1H, brs) 6.90-7.50(8H, m) 4.79(2H, s) 1.00-2.00(15, m) 0.83(6H, d, J=6.6Hz)
40		51 - 52	8.30(1H, dd, J=1.5, 8.4Hz) 8.00(1H, brs) 7.40(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.33(1H, dd, J=1.5, 7.8Hz) 7.06(1H, dt, J=1.5, 7.8Hz) 2.88(1H, m) 1.94-1.98(2H, m) 1.07-1.51(13H, m) 1.24(6H, d, J=7.0Hz) 0.85(6H, d, J=6.6Hz)
41		95 - 96	8.35(1H, dd, J=1.5, 8.4Hz) 7.87(1H, brs) 7.48(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.37(1H, dd, J=1.5, 7.8Hz) 7.31(2H, m) 7.14(1H, dt, J=1.5, 7.8Hz) 6.93(2H, m) 4.78(2H, s) 1.90-1.94(2H, m) 1.07-1.58(13H, m) 0.83(6H, d, J=6.6Hz)
42		52 - 53	8.31(1H, dd, J=1.5, 8.4Hz) 8.09(1H, brs) 7.45(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.41(1H, dd, J=1.5, 7.8Hz) 7.10(1H, dt, J=1.5, 7.8Hz) 1.92-2.25(3H, m) 1.00-1.75(17H, m) 0.86(6H, d, J=6.6Hz)

Table 14

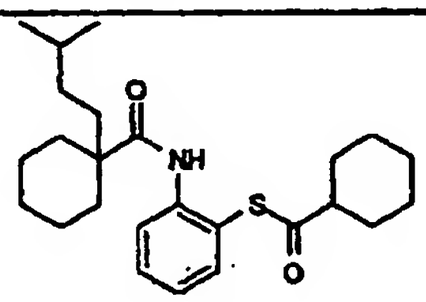
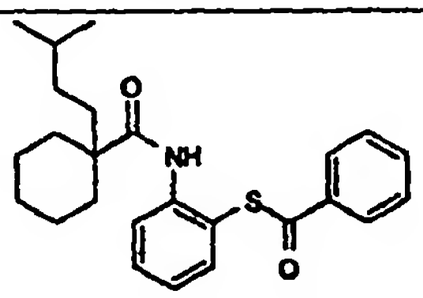
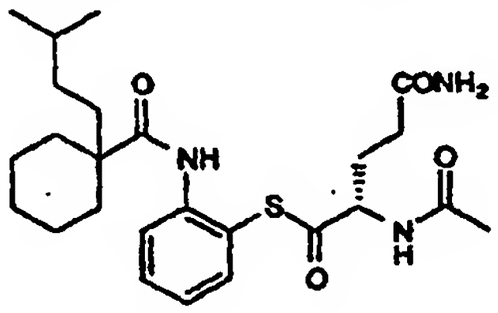
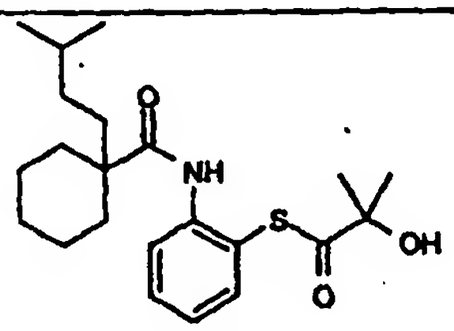
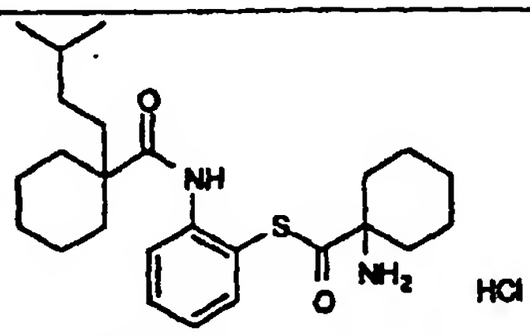
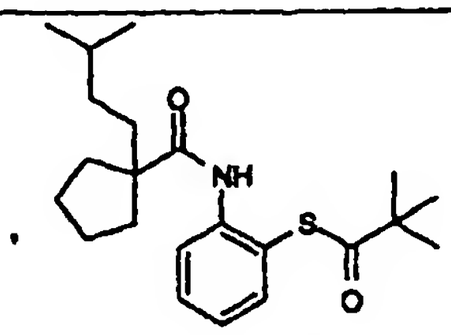
Example	Compound	m.p. (℃)	^{1}H NMR ($CDCl_3$ 300MHz)
4 3		Oil	8.36(1H, dd, J=1.5, 8.4Hz) 8.05(1H, brs) 7.44(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.37(1H, dd, J=1.5, 7.8Hz) 7.12(1H, dt, J=1.5, 7.8Hz) 2.55-2.75(1H, m) 1.95-2.10(4H, m) 1.10-1.85(21H, m) 0.85(6H, d, J=6.6Hz)
4 4		Amorphous	8.38(1H, d, J=8.7Hz) 8.15(1H, brs) 8.04-8.08(2H, m) 7.66(1H, m) 7.48-7.55(4H, m) 7.16(1H, dt, J=1.2, 7.8Hz) 1.93-2.14(2H, m) 1.07-1.51(13H, m) 0.78(6H, d, J=6.6Hz)
4 5		136 - 138	8.41(1H, dd, J=1.5, 8.4Hz) 8.01(1H, brs) 7.46(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.34(1H, dd, J=1.5, 7.8Hz) 7.23(1H, d, J=7.1Hz) 7.11(1H, dt, J=1.5, 7.8Hz) 5.72(1H, brs) 5.41(1H, brs) 4.69(1H, m) 1.95-2.58(6H, m) 1.05-1.70(13H, m) 0.85(6H, d, J=6.6Hz)
4 6		91 - 92	8.42(1H, dd, J=1.5, 8.4Hz) 7.99(1H, brs) 7.47(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.37(1H, dd, J=1.5, 7.8Hz) 7.12(1H, dt, J=1.5, 7.8Hz) 2.64(1H, brs) 1.90-2.10(2H, m) 1.05-1.70(13H, m) 1.54(6H, s) 0.86(6H, d, J=6.6Hz)
4 7		144 - 146	9.90(3H, brs) 8.07(1H, dd, J=1.5, 8.4Hz) 7.98(1H, s) 7.42(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.41(1H, dd, J=1.5, 7.8Hz) 7.10(1H, dt, J=1.5, 7.8Hz) 1.95-2.20(2H, m) 1.10-1.85(21H, m) 0.84(6H, d, J=6.6Hz)
4 8		45 - 46	8.37(1H, dd, J=1.5, 8.4Hz) 7.93(1H, brs) 7.43(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.35(1H, dd, J=1.5, 7.8Hz) 7.09(1H, dt, J=1.5, 7.8Hz) 2.05-2.20(2H, m) 1.45-1.75(9H, m) 1.36(9H, s) 1.10-1.25(2H, m) 0.86(6H, d, J=6.6Hz)

Table 15

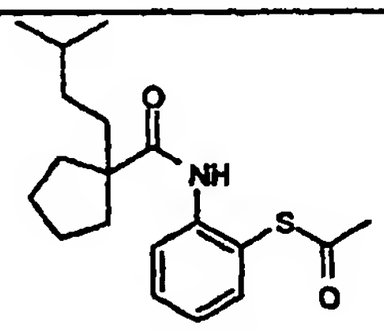
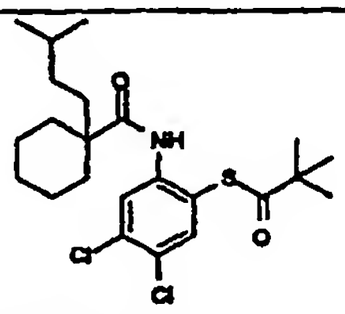
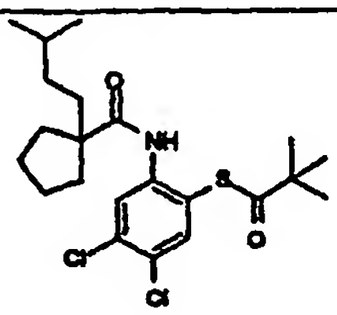
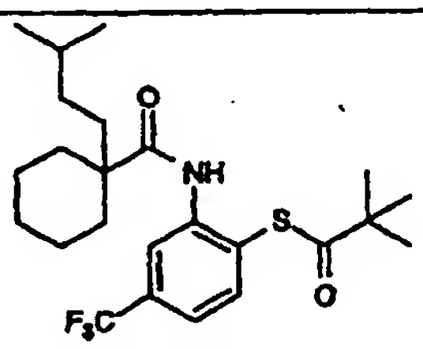
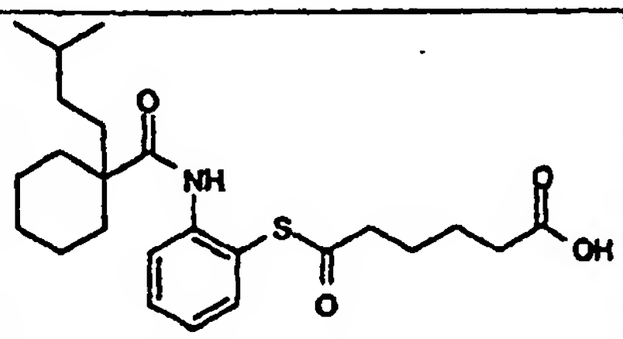
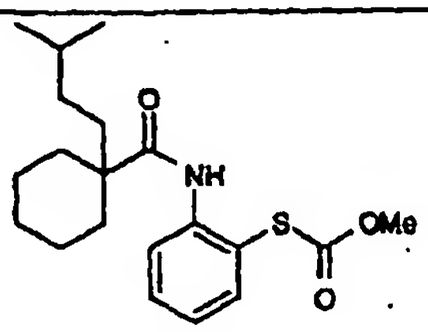
Example	Compound	m.p. (℃)	^{1}H NMR ($CDCl_3$ 300MHz)
4 9		50 - 51	8.33(1H, dd, J=1.5, 8.4Hz) 7.95(1H, brs) 7.46(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.40(1H, dd, J=1.5, 7.8Hz) 7.12(1H, dt, J=1.5, 7.8Hz) 2.46(3H, s) 2.05-2.25(2H, m) 1.40-1.80(9H, m) 1.10-1.25(2H, m) 0.87(6H, d, J=6.6Hz)
5 0		129 - 130	8.72(1H, s) 8.01(1H, brs) 7.44(1H, s) 1.90-2.10(2H, m) 1.10-1.75(13H, m) 1.35(9H, s) 0.85(6H, d, J=6.6Hz)
5 1		66 - 67	8.68(1H, s) 7.88(1H, brs) 7.43(1H, s) 2.05-2.20(2H, m) 1.30-1.75(9H, m) 1.35(9H, s) 1.05-1.20(2H, m) 0.86(6H, d, J=6.6Hz)
5 2		69 - 71	8.82(1H, d, J=1.5Hz) 8.16(1H, brs) 7.48(1H, d, J=8.1Hz) 7.34(1H, dd, J=1.5, 8.1Hz) 1.90-2.15(2H, m) 1.05-1.75(13H, m) 1.37(9H, s) 0.86(6H, d, J=6.6Hz)
5 3		Oil	8.35(1H, dd, J=1.5, 8.4Hz) 8.05(1H, brs) 7.47(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.39(1H, dd, J=1.5, 7.8Hz) 7.13(1H, dt, J=1.5, 7.8Hz) 2.74(2H, t, J=6.9Hz) 2.40(2H, t, J=6.9Hz) 1.90-2.10(2H, m) 1.05-1.90(17H, m) 0.86(6H, d, J=6.6Hz)
5 4		Oil	8.39(1H, dd, J=1.5, 8.4Hz) 8.27(1H, brs) 7.52(1H, dd, J=1.5, 7.8Hz) 7.47(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.11(1H, dt, J=1.5, 7.8Hz) 3.84(3H, s) 2.00-2.10(2H, m) 1.10-1.65(13H, m) 0.85(6H, d, J=6.6Hz)

Table 16

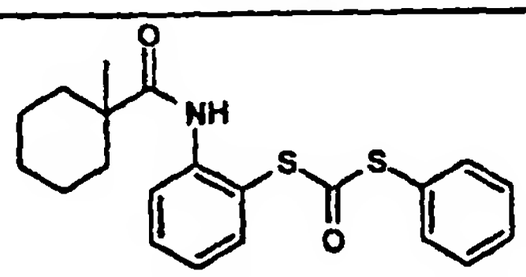
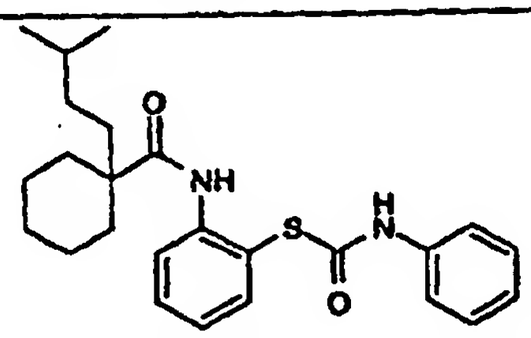
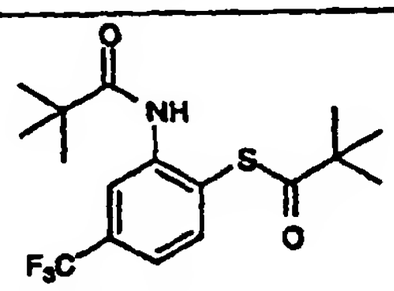
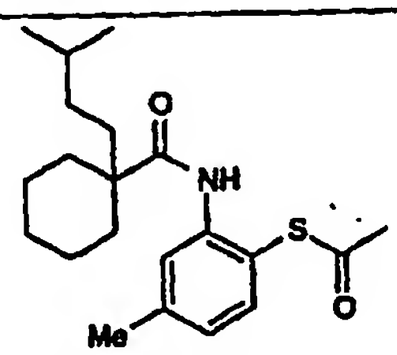
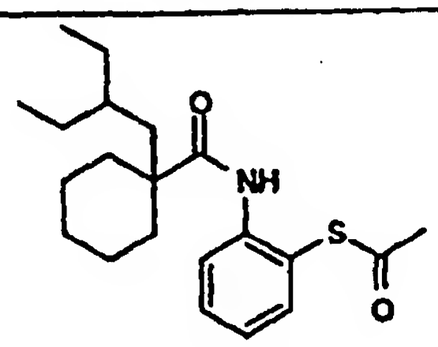
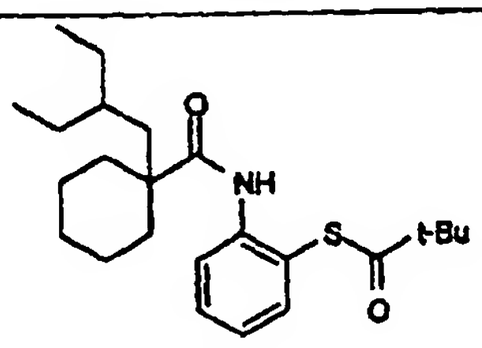
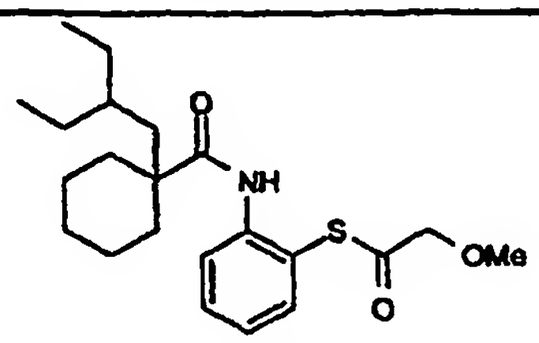
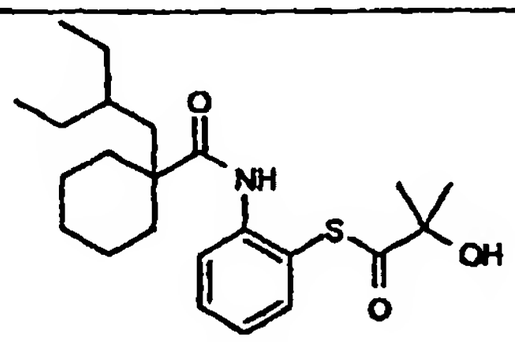
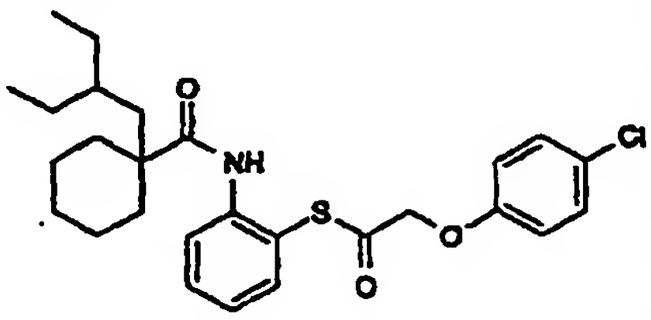
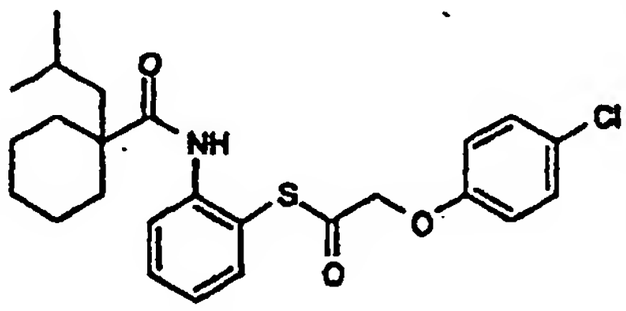
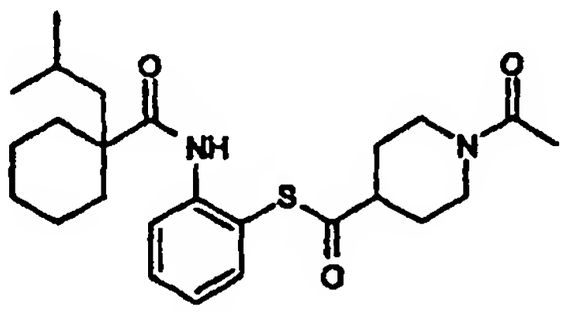
Example	Compound	m.p. (℃)	^{1}H NMR ($CDCl_3$ 300MHz)
55		Oil	8.44(1H, dd, J=1.5, 8.4Hz) 8.29(1H, brs) 7.35-7.55(7H, m) 7.13(1H, dt, J=1.5, 7.8Hz) 1.95-2.15(2H, m) 1.25-1.70(8H, m) 1.27(3H, s)
56		40 - 41	8.58(1H, brs) 8.42(1H, dd, J=1.5, 7.7Hz) 7.61(1H, dd, J=1.5, 7.7Hz) 7.53(1H, dt, J=1.5, 7.7Hz) 7.10-7.35(7H, m) 2.03-2.09(2H, m) 1.09-1.59(13H, m) 0.78(6H, d, J=6.6Hz)
57		103	8.80(1H, d, J=1.5Hz) 8.16(1H, brs) 7.48(1H, d, J=8.1Hz) 7.35(1H, dd, J=1.5, 7.8Hz) 1.37(9H, s) 1.30(9H, s)
58		Oil	8.22(1H, d, J=1.5Hz) 8.03(1H, brs) 7.26(1H, d, J=7.8Hz) 6.93(1H, dd, J=1.5, 7.8Hz) 2.43(3H, s) 2.38(3H, s) 1.10-2.10(15H, m) 0.85(6H, d, J=6.6Hz)
59		76.5 - 79.0	8.38(1H, dd, J=1.5, 8.4Hz) 8.13(1H, brs) 7.47(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.40(1H, dd, J=1.5, 7.8Hz) 7.12(1H, dt, J=1.5, 7.8Hz) 2.46(3H, s) 2.00-2.15(2H, m) 1.15-1.70(15H, m) 0.79(6H, t, J=6.9Hz)
60		64.5 - 66.5	8.42(1H, dd, J=1.5, 8.4Hz) 8.11(1H, brs) 7.45(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.36(1H, dd, J=1.5, 7.8Hz) 7.10(1H, dt, J=1.5, 7.8Hz) 1.95-2.15(2H, m) 1.10-1.75(15H, m) 1.36(9H, s) 0.79(6H, t, J=6.9Hz)

Table 17

Example	Compound	m.p. (℃)	^{1}H NMR ($CDCl_3$ 300MHz)
6 1		67.5 - 69.5	8.40(1H, dd, J=1.5, 8.4Hz) 8.06(1H, brs) 7.47(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.39(1H, dd, J=1.5, 7.8Hz) 7.13(1H, dt, J=1.5, 7.8Hz) 4.20(2H, s) 3.59(3H, s) 1.95-2.15(2H, m) 1.10-1.75(15H, m) 0.79(6H, t, J=6.9Hz)
6 2		68.0 - 70.0	8.44(1H, dd, 1.5, 8.4Hz) 8.06(1H, brs) 7.47(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.37(1H, dd, J=1.5, 7.8Hz) 7.12(1H, dt, J=1.5, 7.8Hz) 2.61(1H, s) 2.00-2.15(2H, m) 1.15-1.75(15H, m) 1.54(6H, s) 0.78(6H, t, J=6.9Hz)
6 3		62.0 - 63.0	8.39(1H, dd, J=1.5, 8.4Hz) 7.95(1H, brs) 7.48(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.38(1H, dd, J=1.5, 7.8Hz) 7.32(2H, m) 7.14(1H, dt, J=1.5, 7.8Hz) 6.94(2H, m) 4.78(2H, s) 1.85-2.05(2H, m) 1.15-1.70(15H, m) 0.77(6H, t, J=6.9Hz)
6 4		61.0 - 65.0	8.40(1H, dd, J=1.5, 8.4Hz) 7.92(1H, brs) 7.49(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.39(1H, dd, J=1.5, 7.8Hz) 7.33(2H, m) 7.15(1H, dt, J=1.5, 7.8Hz) 6.96(2H, m) 4.80(2H, s) 1.85-2.00(2H, m) 1.20-1.80(11H, m) 0.86(6H, d, J=6.6Hz)
6 5		61.0 - 64.0	8.38(1H, dd, J=1.5, 8.4Hz) 8.02(1H, brs) 7.47(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.37(1H, dd, J=1.5, 7.8Hz) 7.12(1H, dt, J=1.5, 7.8Hz) 4.59(1H, m) 3.88(1H, m) 3.17(1H, m) 2.92(1H, m) 2.78(1H, m) 1.90-2.20(4H, m) 2.11(3H, s) 1.20-1.85(13H, m) 0.87(6H, d, J=6.6Hz)

[0134] The compounds 25-1 through 25-109 shown in Tables 18 through 27 were obtained in the same manner as in Examples 25 through 28.

Table 18

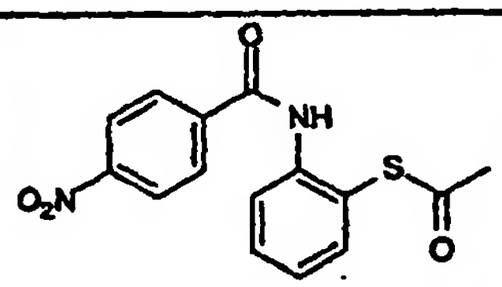
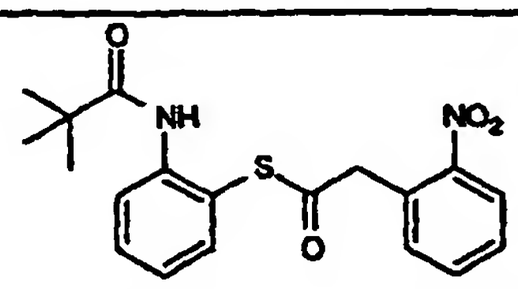
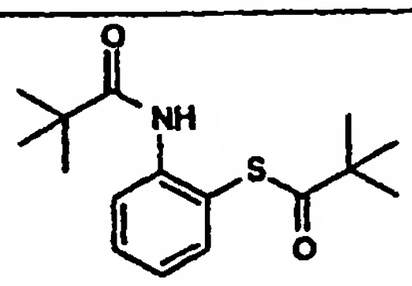
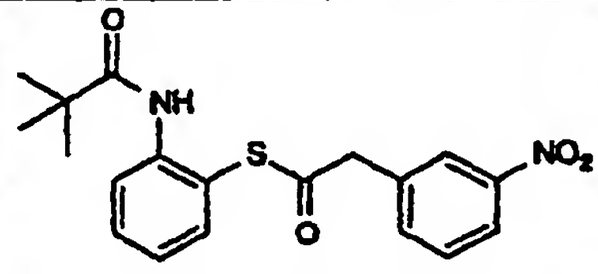
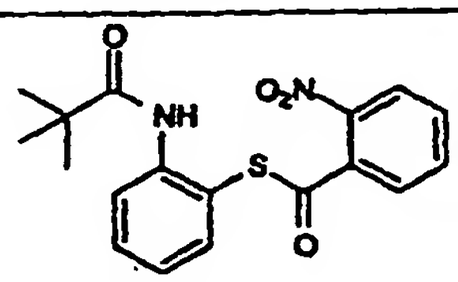
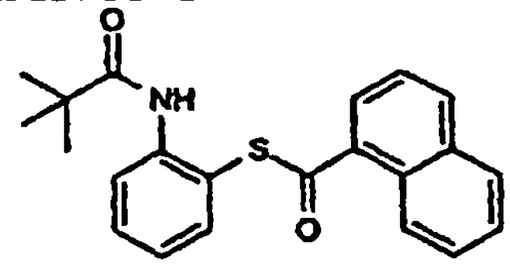
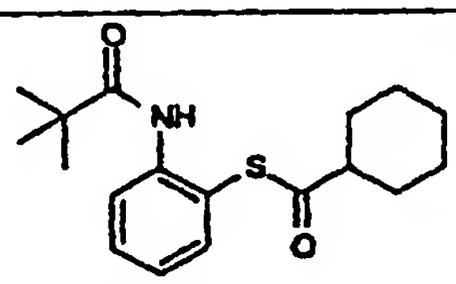
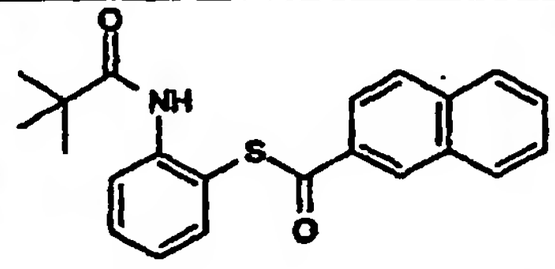
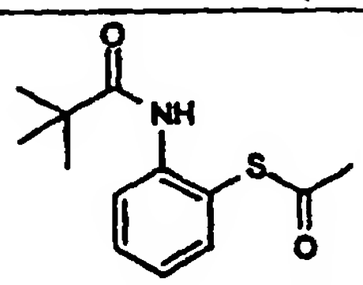
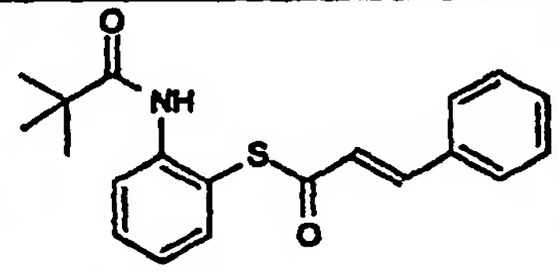
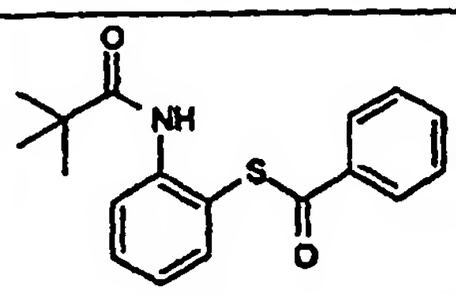
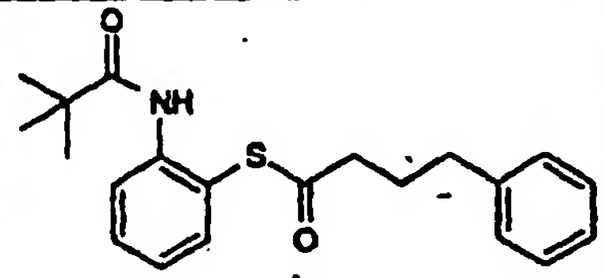
No.	Compound	No.	Compound
25-1		25-7	
25-2		25-8	
25-3		25-9	
25-4		25-10	
25-5		25-11	
25-6		25-12	

Table 19

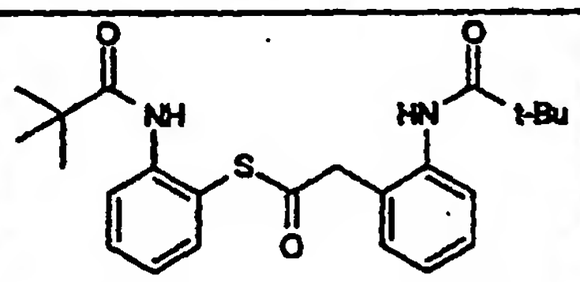
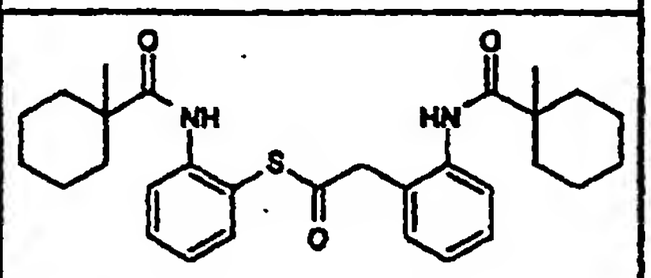
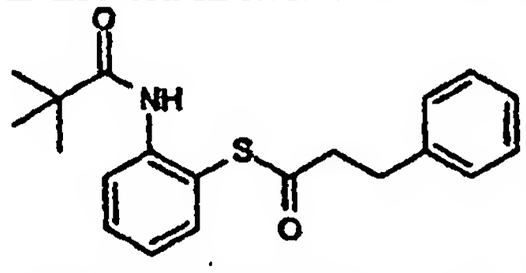
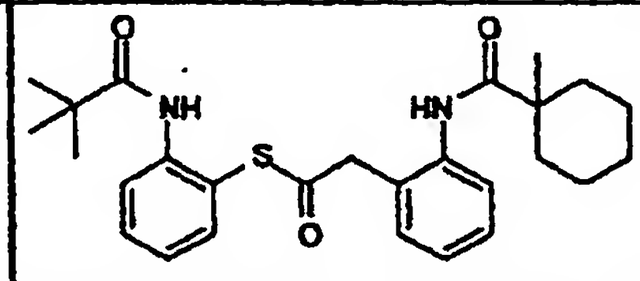
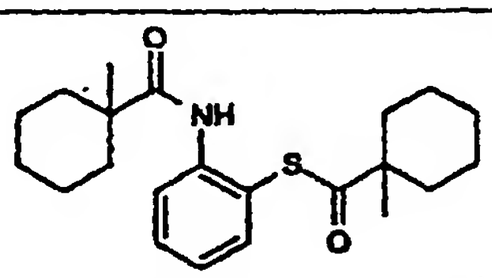
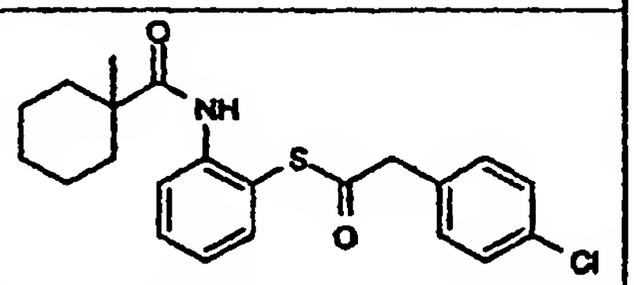
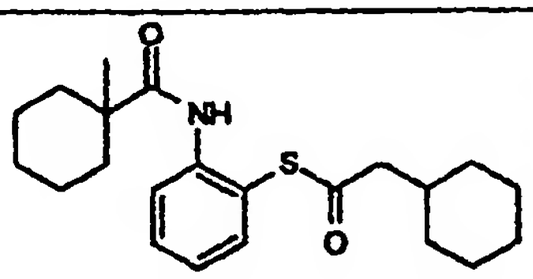
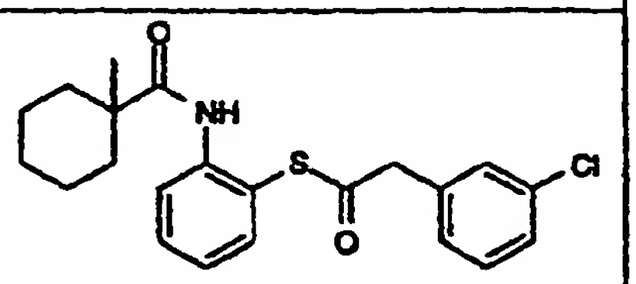
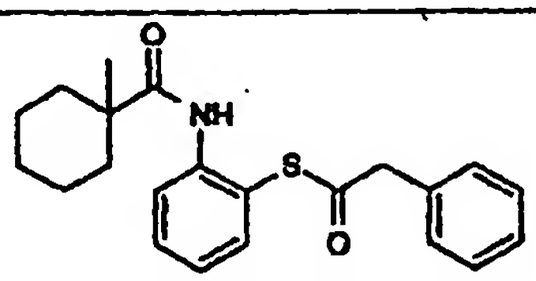
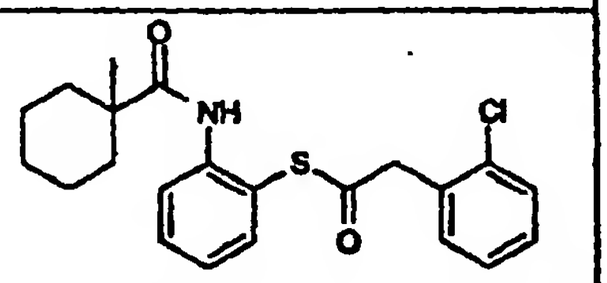
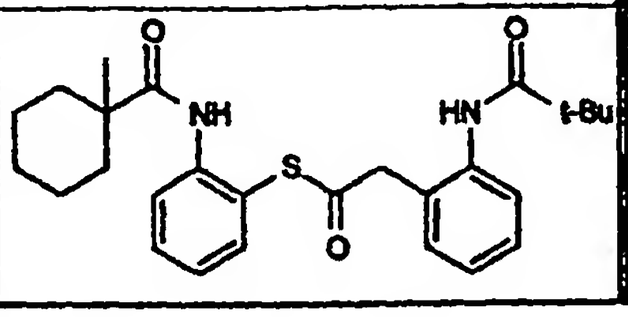
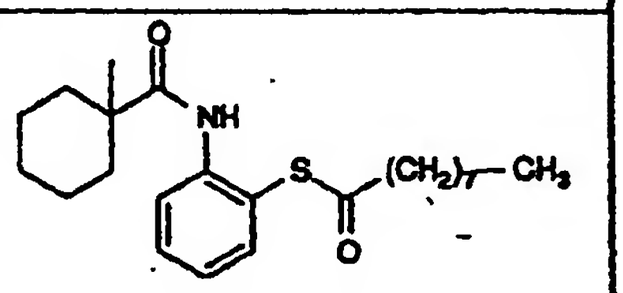
No.	Compound	No.	Compound
25-13		25-19	
25-14		25-20	
25-15		25-21	
25-16		25-22	
25-17		25-23	
25-18		25-24	

Table 20

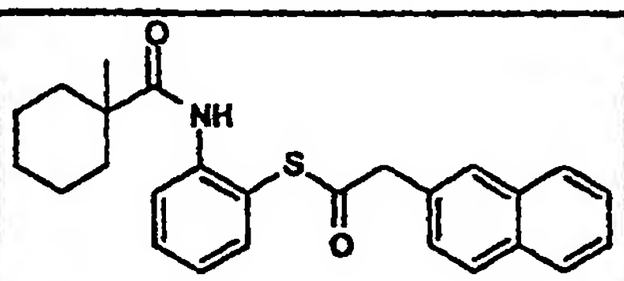
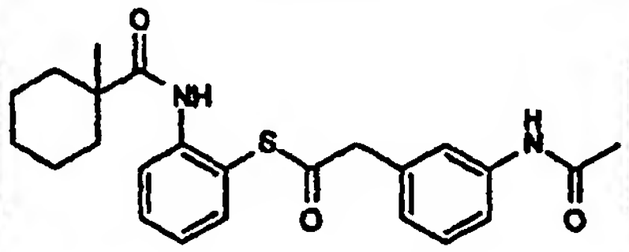
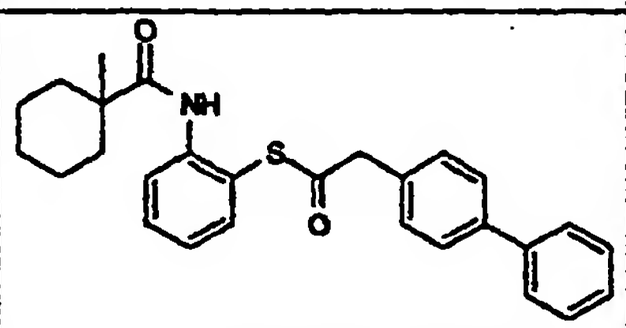
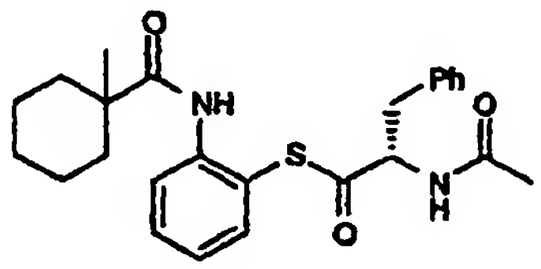
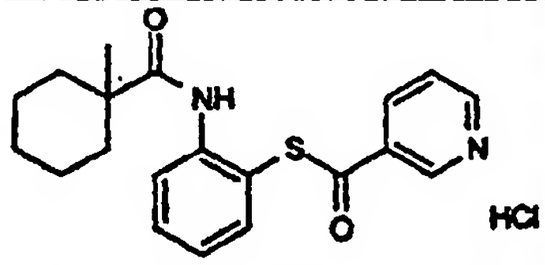
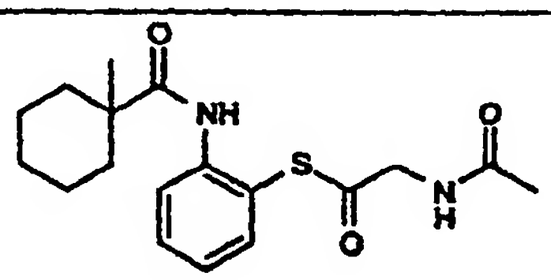
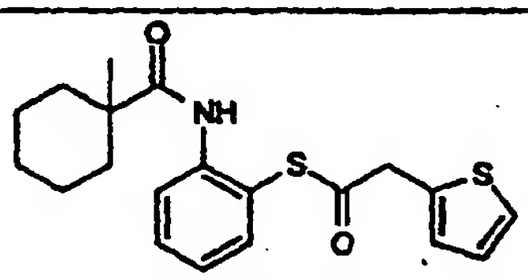
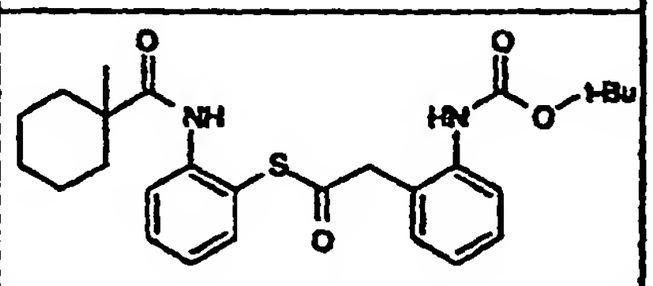
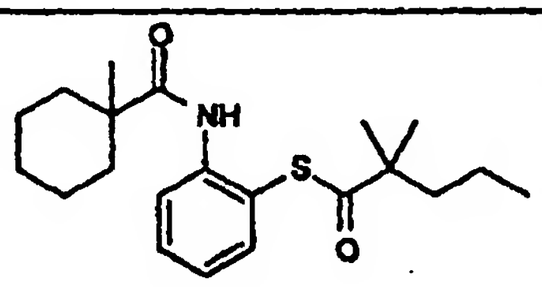
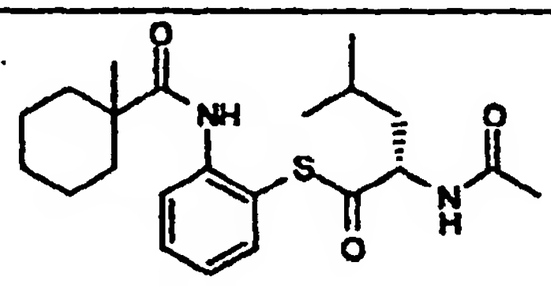
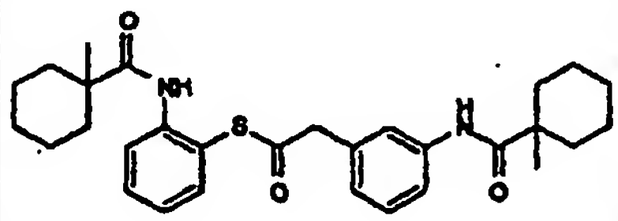
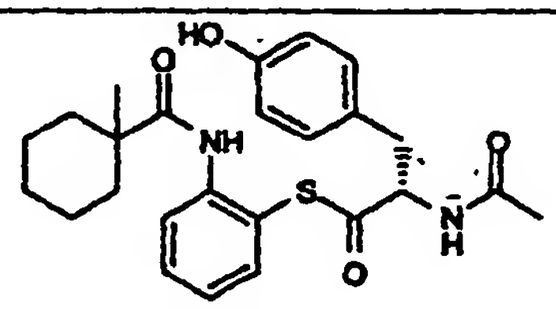
No.	Compound	No.	Compound
25-25		25-31	
25-26		25-32	
25-27		25-33	
25-28		25-34	
25-29		25-35	
25-30		25-36	

Table 21

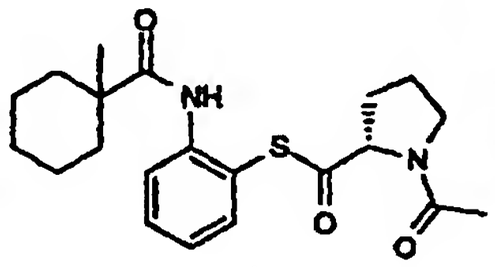
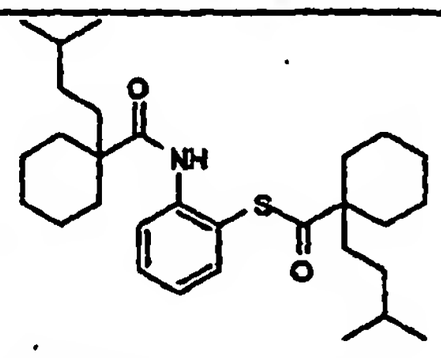
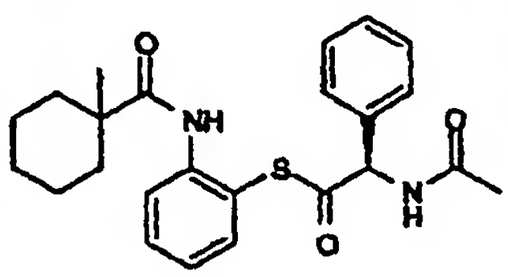
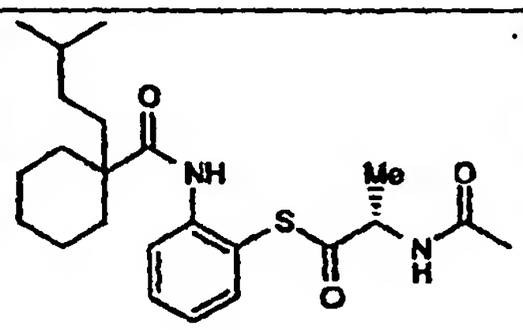
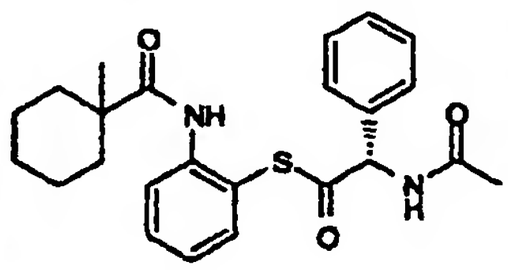
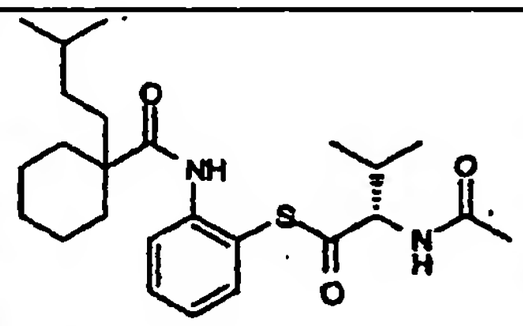
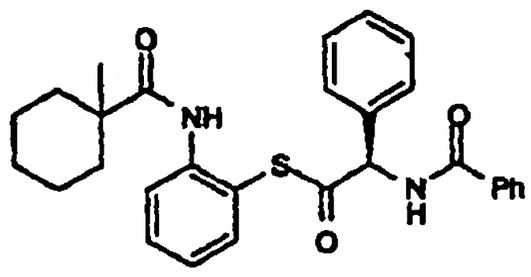
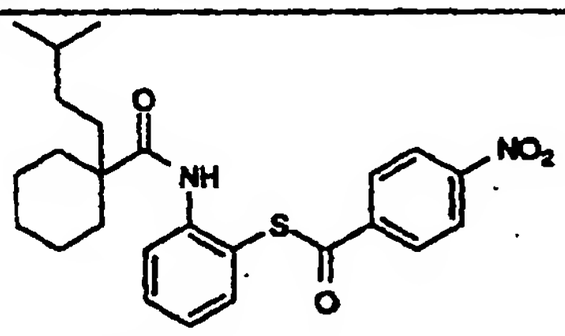
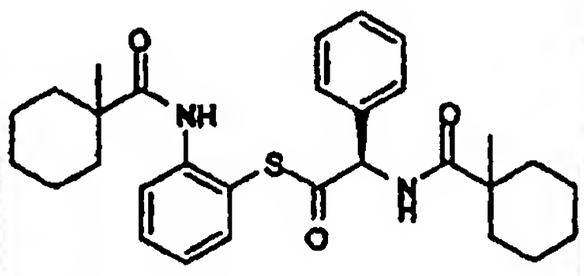
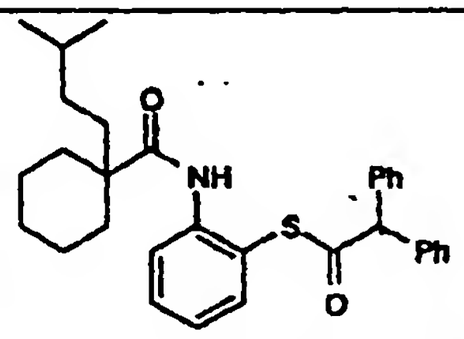
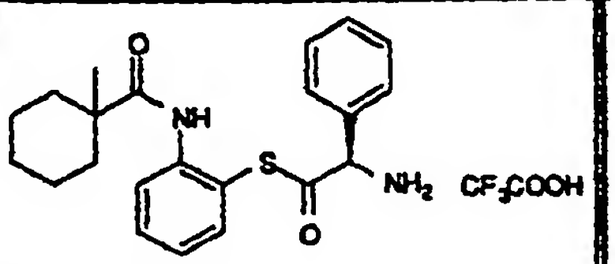
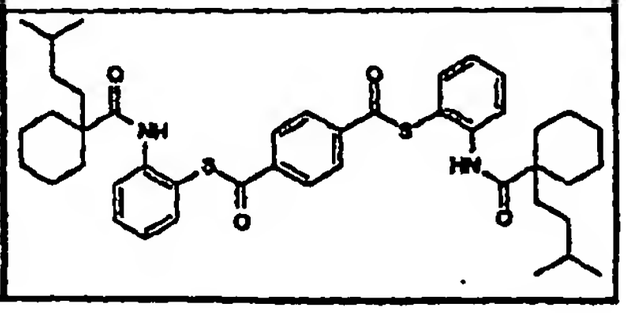
No.	Compound	No.	Compound
25-37		25-43	
25-38		25-44	
25-39		25-45	
25-40		25-46	
25-41		25-47	
25-42		25-48	

Table 22

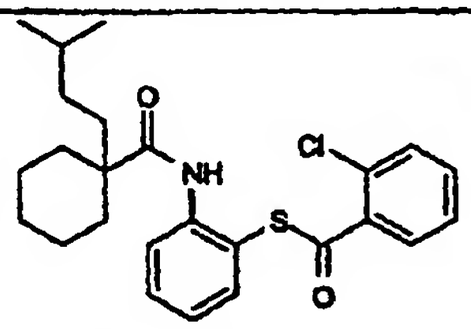
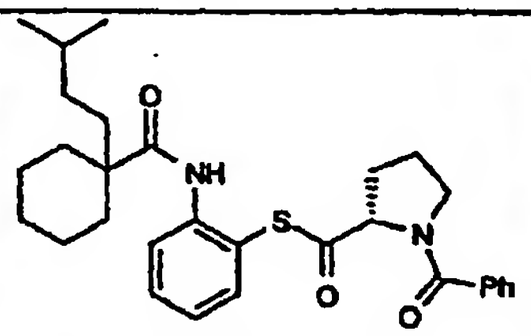
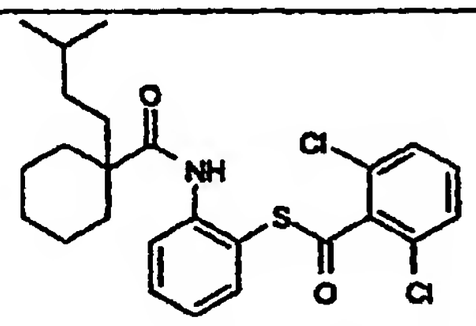
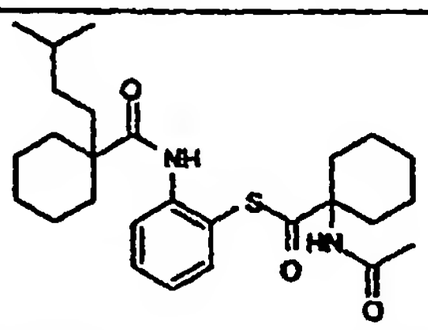
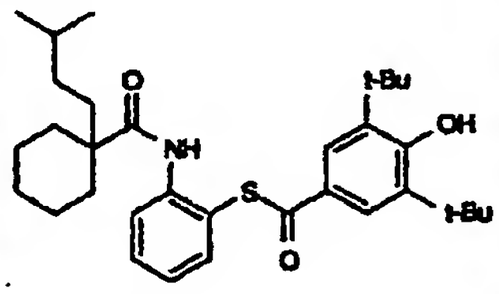
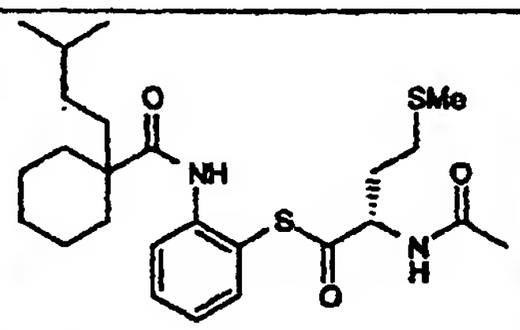
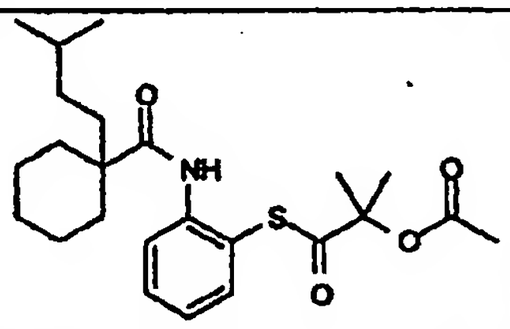
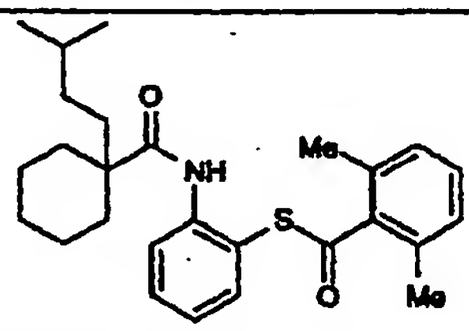
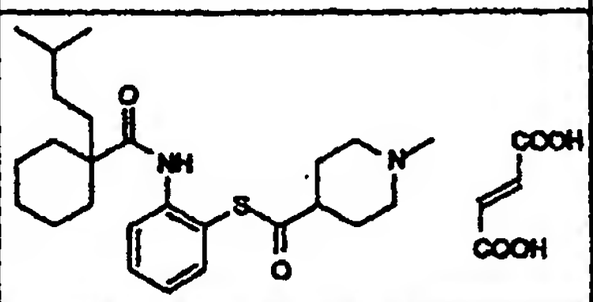
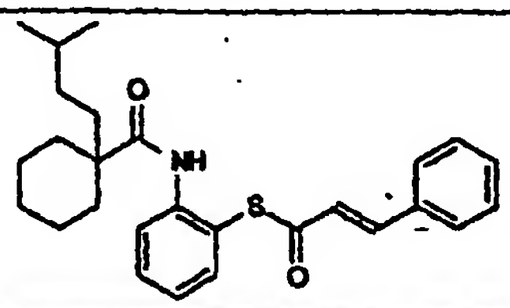
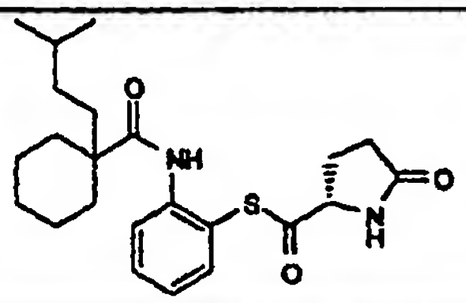
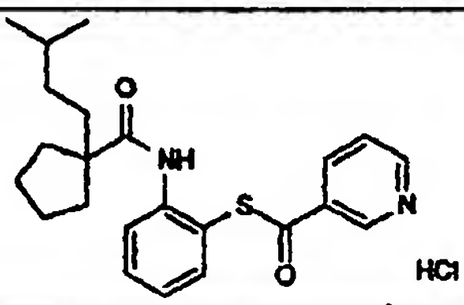
No.	Compound	No.	Compound
25-49		25-55	
25-50		25-56	
25-51		25-57	
25-52		25-58	
25-53		25-59	
25-54		25-60	

Table 23

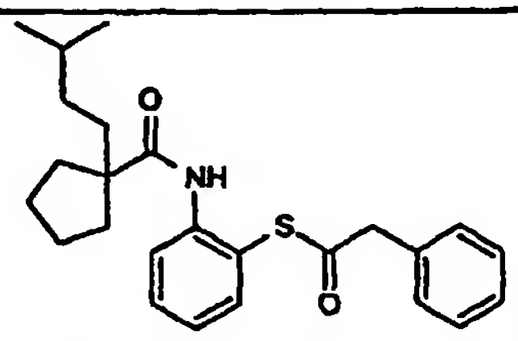
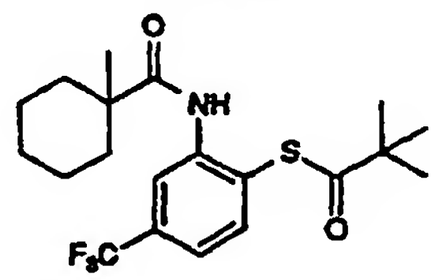
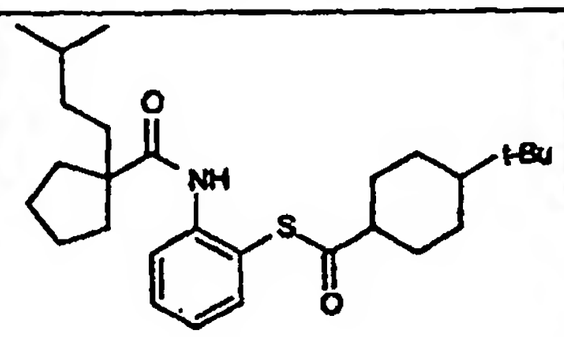
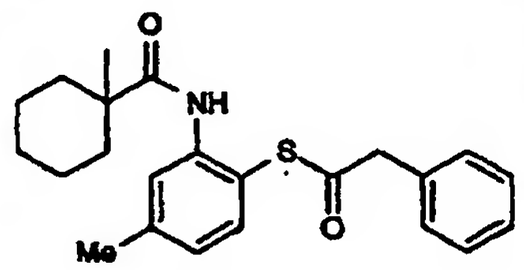
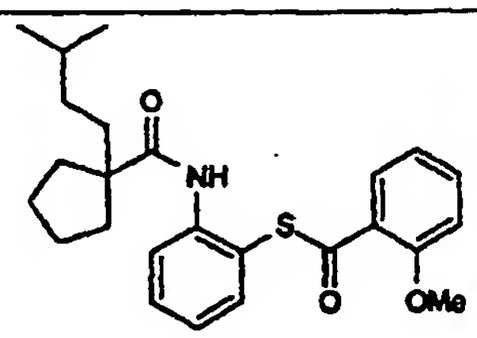
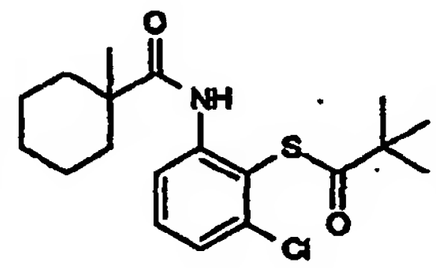
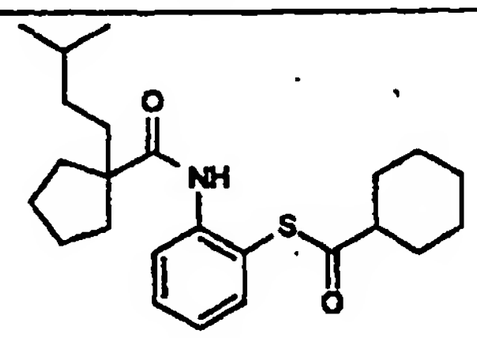
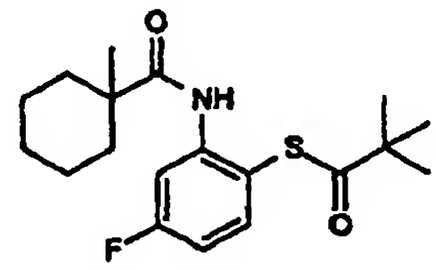
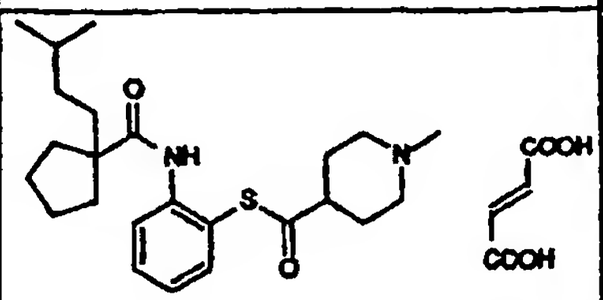
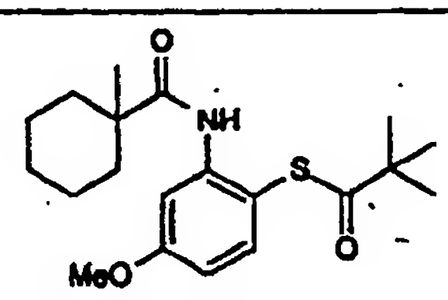
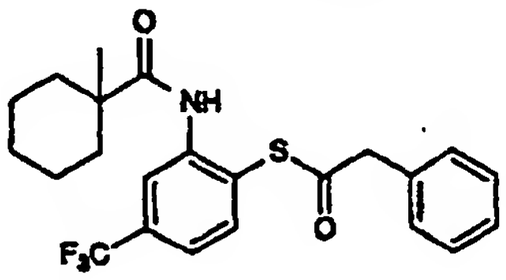
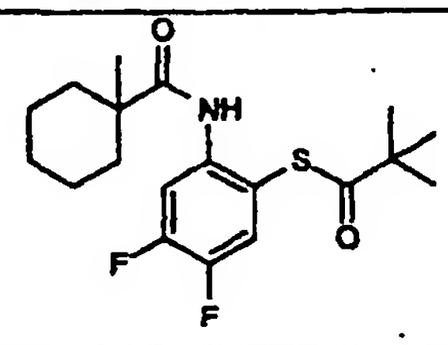
No.	Compound	No.	Compound
25-61		25-67	
25-62		25-68	
25-63		25-69	
25-64		25-70	
25-65		25-71	
25-66		25-72	

Table 24

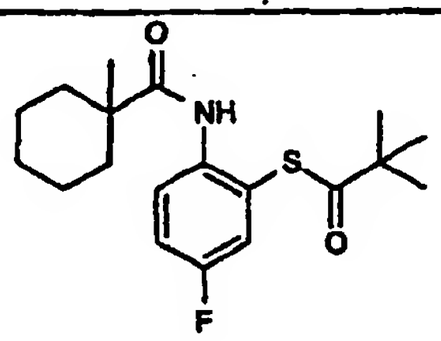
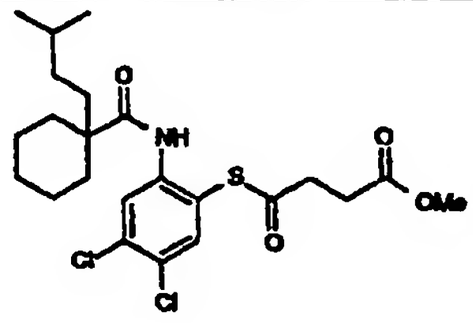
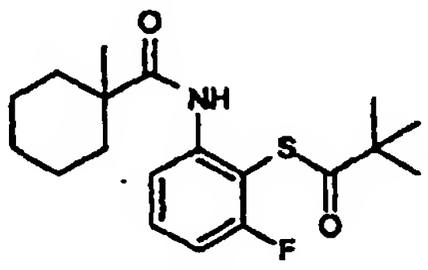
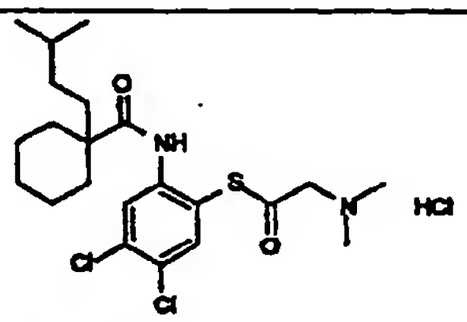
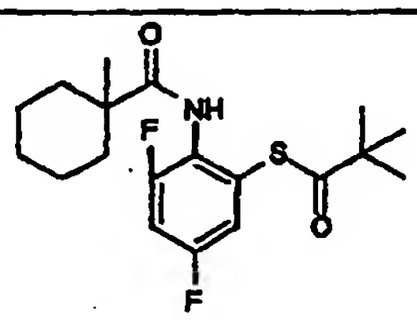
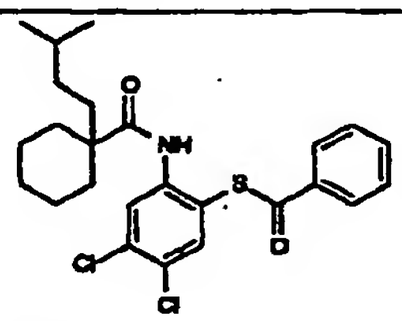
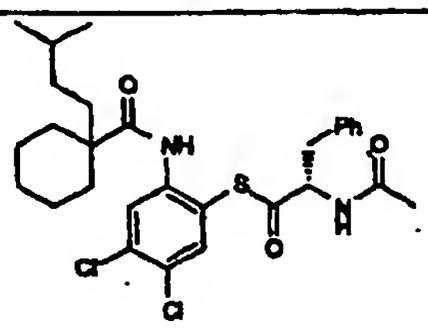
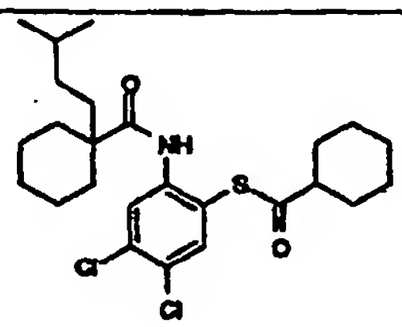
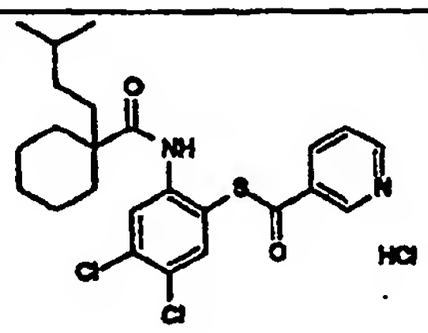
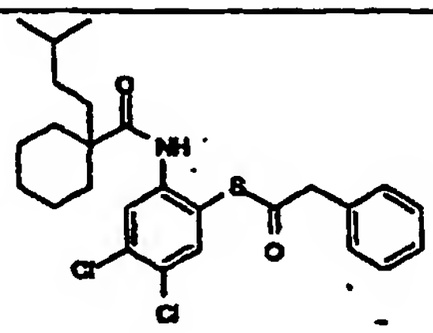
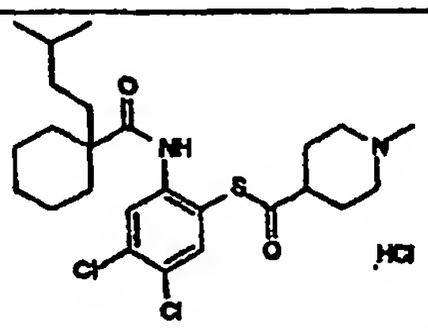
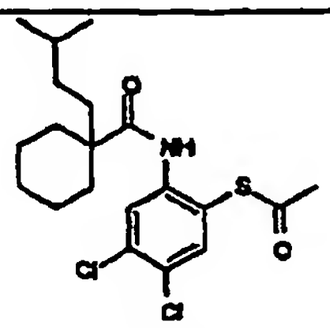
No.	Compound	No.	Compound
25-73		25-79	
25-74		25-80	
25-75		25-81	
25-76		25-82	
25-77		25-83	
25-78		25-84	

Table 25

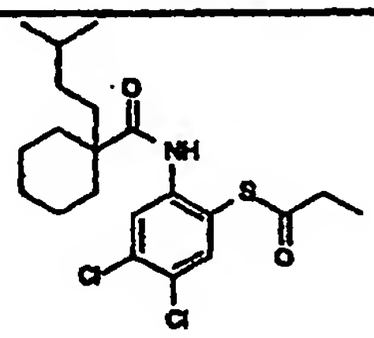
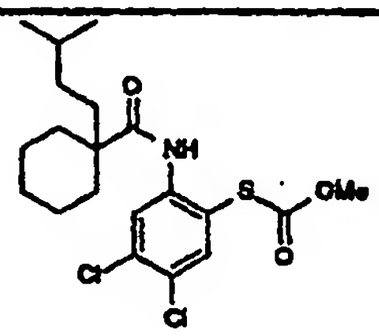
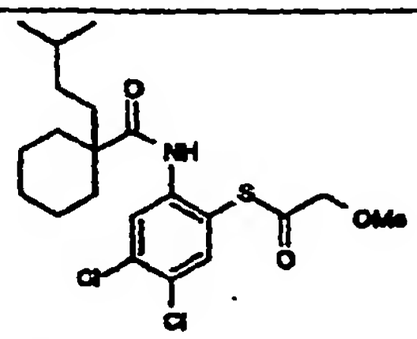
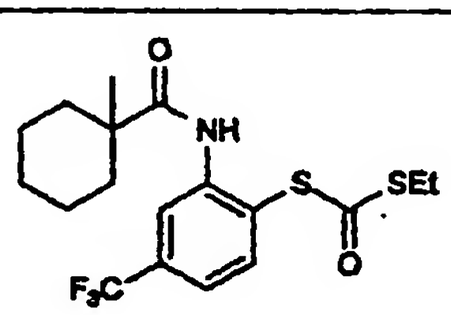
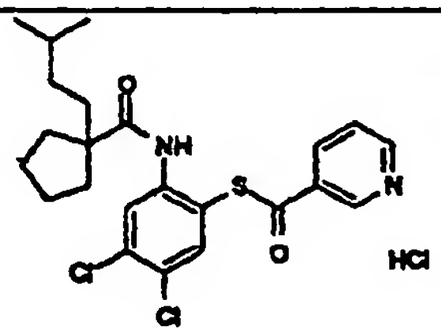
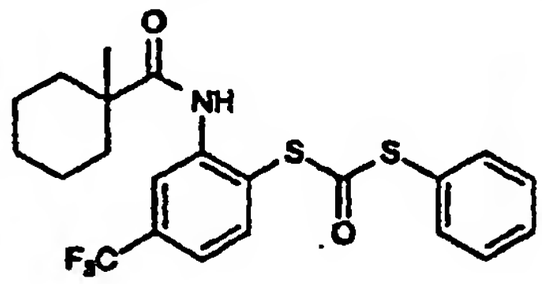
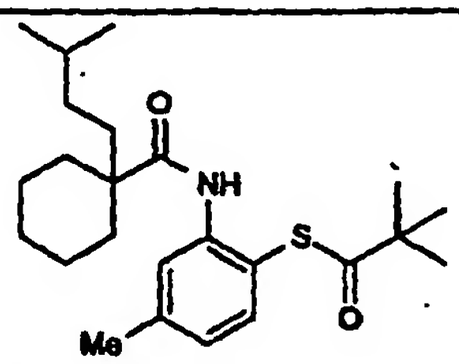
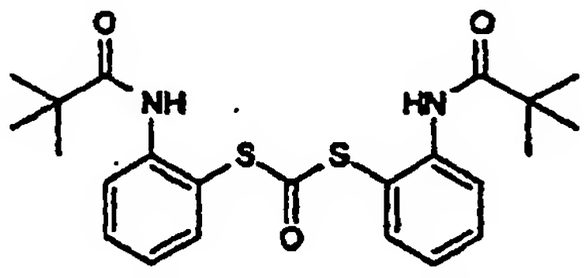
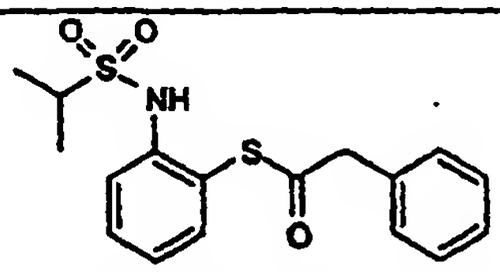
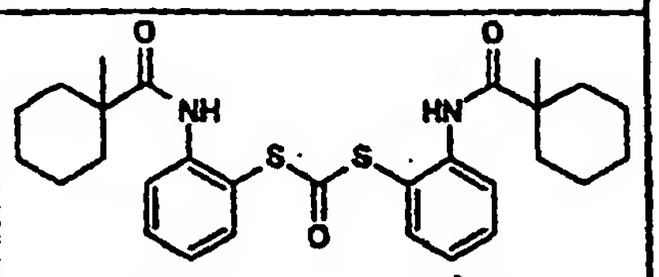
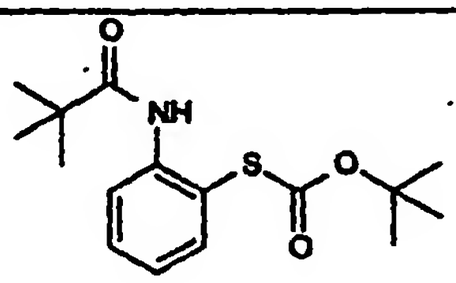
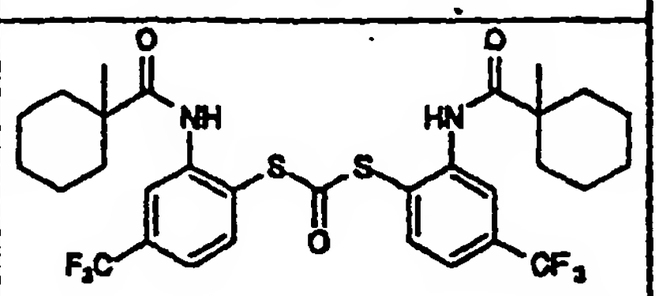
No.	Compound	No.	Compound
25-85		25-91	
25-86		25-92	
25-87		25-93	
25-88		25-94	
25-89		25-95	
25-90		25-96	

Table 26.

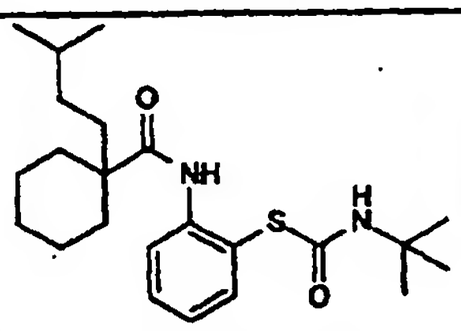
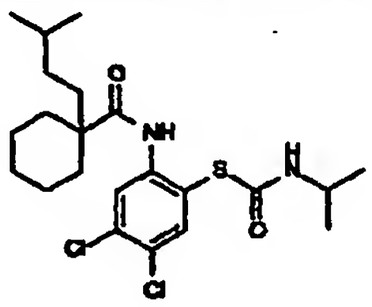
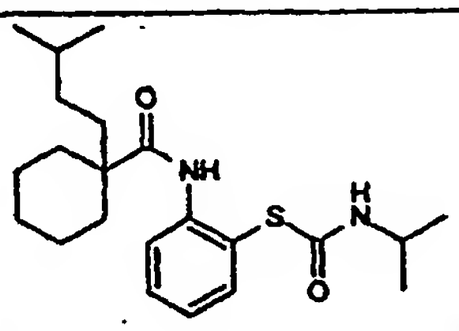
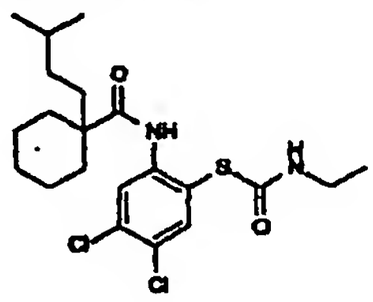
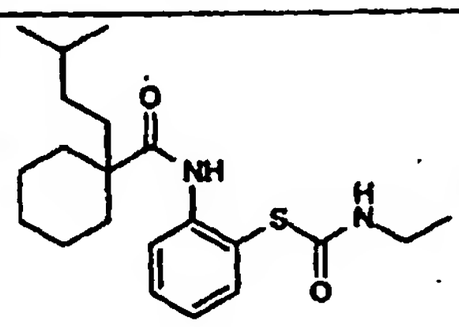
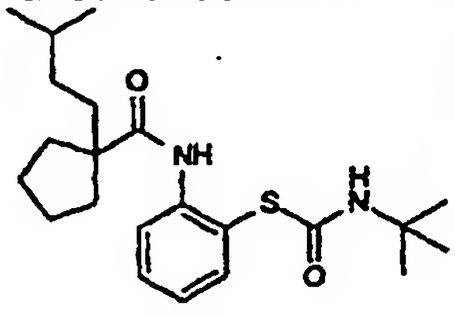
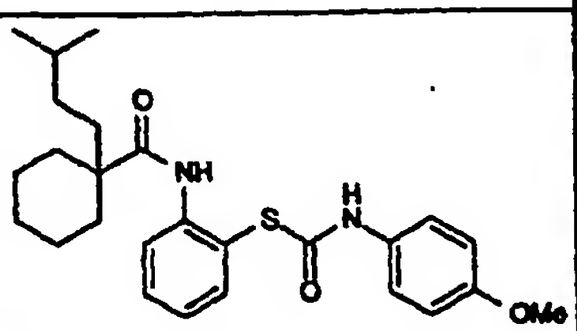
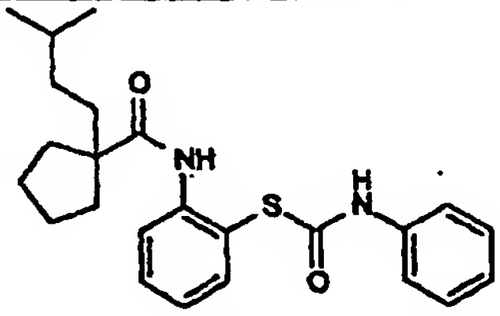
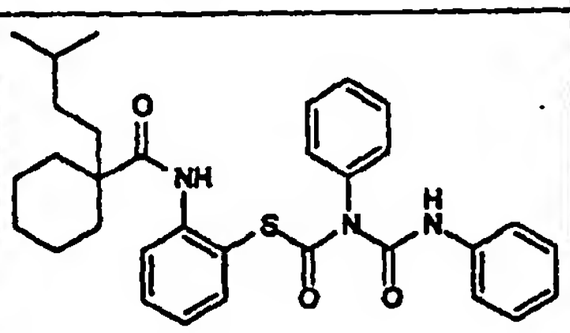
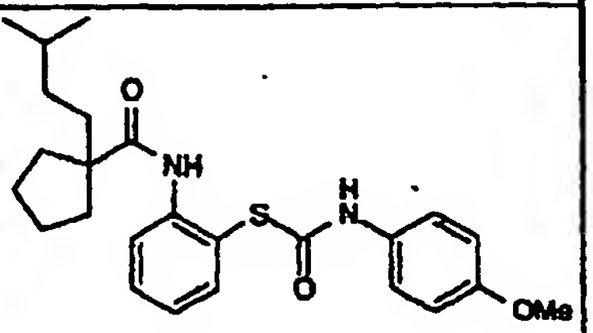
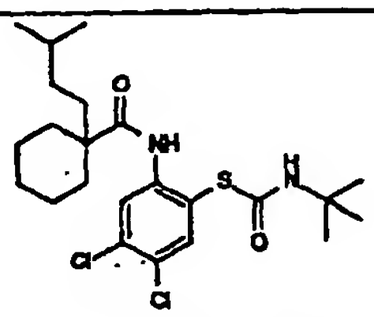
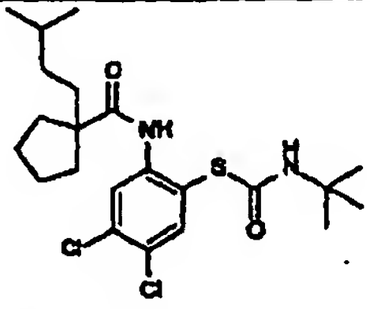
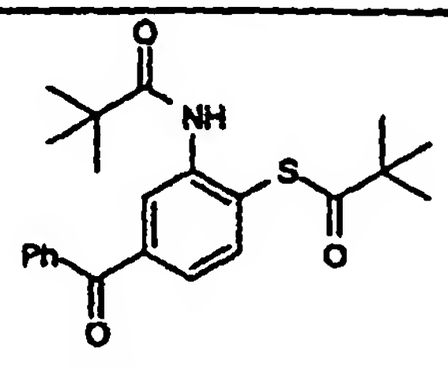
No.	Compound	No.	Compound
25-97		25-103	
25-98		25-104	
25-99		25-105	
25-100		25-106	
25-101		25-107	
25-102		25-108	

Table 27

No.	Compound
25-109	

Example 66

Synthesis of S-[4,5-dichloro-2-(1-isopropylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate (formula (I); R=1-isopropylcyclohexyl, X_1, X_4 =a hydrogen atom, X_2, X_3=a chlorine atom, Y=carbonyl, Z=pivaloyl).

[0135] Step 4) A tetrahydrofuran (0.5 ml)-methanol (1 ml) solution containing S-[4,5-dichloro-2-(1-isopropylcyclohexanecarbonylamino)phenyl] N,N-dimethylthiocarbamate (86 mg) obtained in the same manner as in the step 9) of Example 19 and potassium hydroxide (50 mg) was refluxed for 30 minutes under heating. After the solution was allowed to cool, water was added and the aqueous layer was washed with hexane. Then, the aqueous layer was acidified with potassium hydrogensulfate, and was extracted with chloroform (10 ml). Pyridine (90 µl) was added to the resulting extract, and pivaloyl chloride (41 µl) was further added to the extract at room temperature under stirring. The solution was stirred for 1 hour. After concentration, the residue was purified by silica gel column chromatography (a developing solvent; hexane : ethyl acetate=20:1) to obtain the desired compound (24 mg, yield: 27 %).

Examples 67-81

[0136] The compounds shown in Tables 2 8-30 were obtained in the same manner as in Example 66.

Table 28

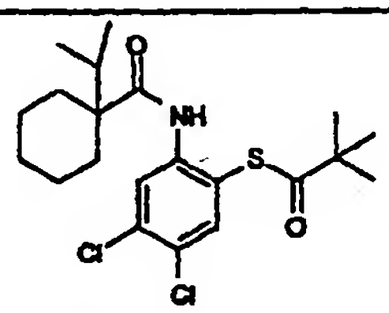
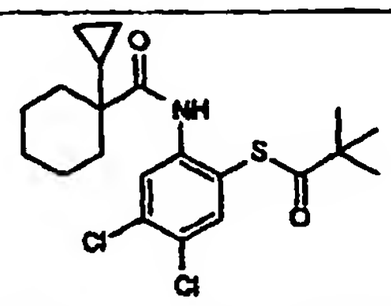
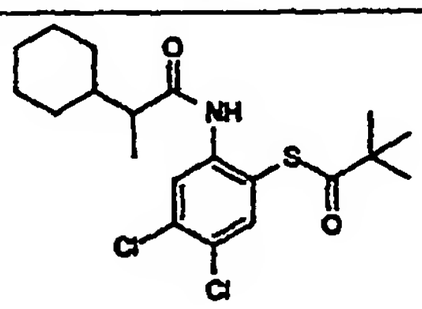
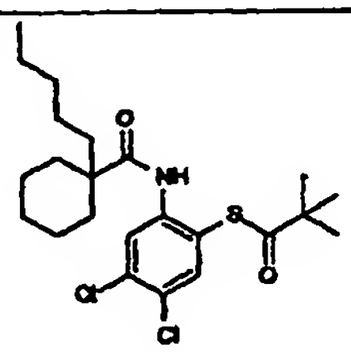
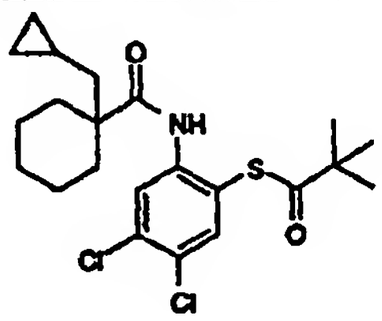
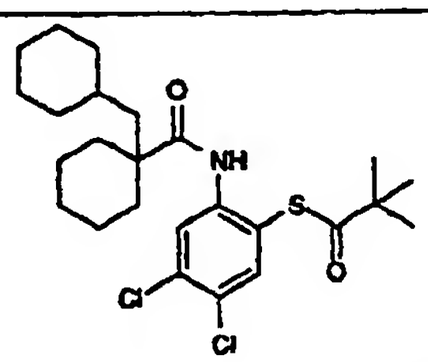
Example	Compound	m.p. (℃)	^{1}H NMR ($CDCl_3$ 300MHz)
66		92 - 92	8.75(1H, s) 8.01(1H, brs) 7.44(1H, s) 1.95-2.10(2H, m) 1.10-1.75(9H, m) 1.34(9H, s) 0.91(6H, d, J=6.6Hz)
67		95 - 96	8.73(1H, s) 8.10(1H, brs) 7.44(1H, s) 1.85-2.00(2H, m) 1.10-1.70(8H, m) 1.34(9H, s) 0.89(6H, m) 0.35-0.47(4H, m)
68		109 - 110	8.67(1H, s) 7.61(1H, brs) 7.44(1H, s) 2.06(1H, quint, J=7.2Hz) 0.85-1.85(11H, m) 1.36(9H, s) 1.18(3H, d, J=6.6Hz)
69		109 - 110	8.71(1H, s) 8.01(1H, brs) 7.44(1H, s) 1.95-2.05(2H, m) 1.05-1.70(18H, m) 1.35(9H, s) 0.84(3H, t, J=6.7Hz) 0.84(6H, d, J=6.6Hz)
70		116 - 117	8.76(1H, s) 8.11(1H, brs) 7.44(1H, s) 2.02-2.15(2H, m) 1.20-1.65(8H, m) 1.34(9H, s) 0.55-0.65(1H, m) 0.35-0.45(2H, m) 0.01-0.02(4H, m)
71		111 - 112	8.70(1H, s) 8.03(1H, brs) 7.44(1H, s) 1.90-2.10(2H, m) 0.75-1.75(21H, m) 1.36(9H, s)

Table 29

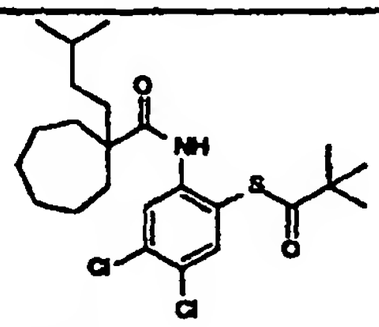
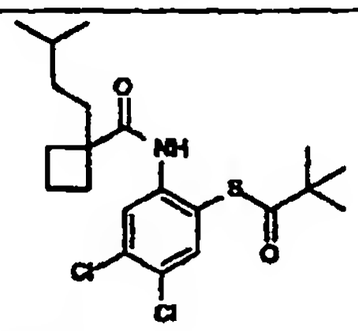
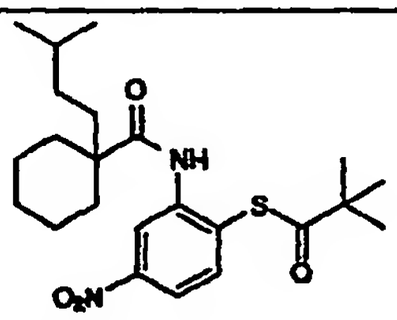
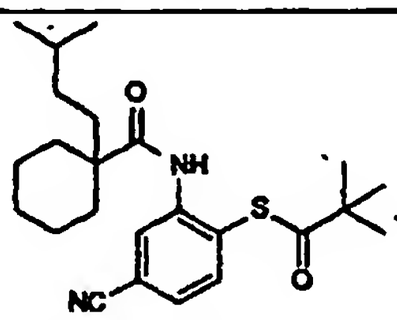
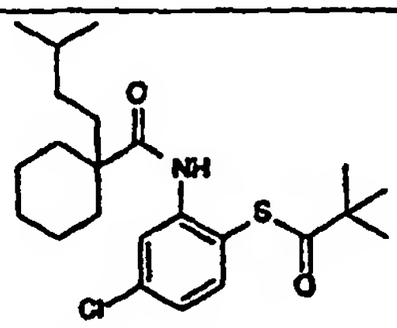
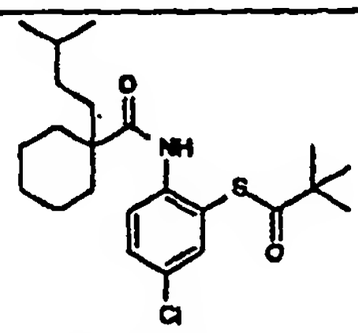
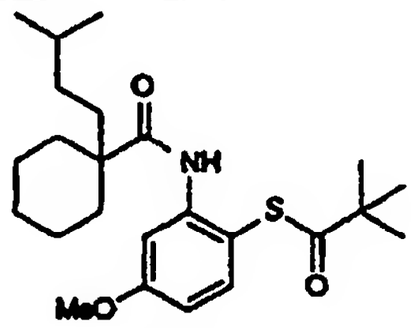
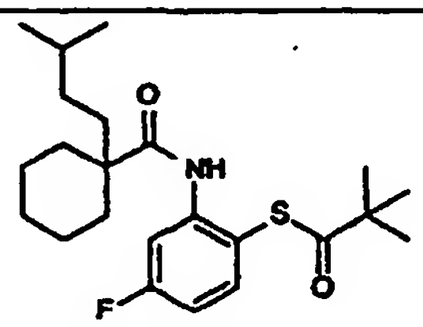
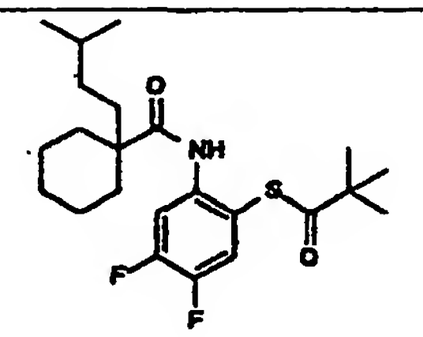
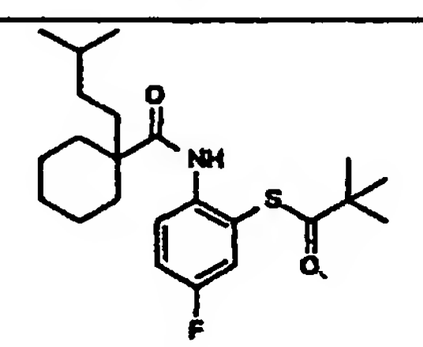
Example	Compound	m.p. (℃)	^{1}H NMR ($CDCl_3$ 300MHz)
72		101 - 102	8.70(1H, s) 7.92(1H, brs) 7.43(1H, s) 2.00-2.15(2H, m) 1.30-1.65(13H, m) 1.35(9H, s) 1.05-1.15(2H, m) 0.85(6H, d, J=6.6Hz)
73		53 - 54	8.70(1H, s) 7.68(1H, brs) 7.44(1H, s) 2.35-2.50(2H, m) 1.25-2.05(7H, m) 1.34(9H, s) 1.05-1.15(2H, m) 0.88(6H, d, J=6.6Hz)
74		93.0 - 93.5	9.39(1H, d, J=2.4Hz) 8.20(1H, brs) 7.93(1H, dd, J=2.4, 8.4Hz) 7.53(1H, d, J=8.4Hz) 1.95-2.15(2H, m) 1.00-1.75(13H, m) 1.37(9H, s) 0.85(6H, d, J=6.6Hz)
75		103 - 104	8.85(1H, d, J=1.5Hz) 8.14(1H, brs) 7.46(1H, d, J=7.8Hz) 7.35(1H, dd, J=1.5, 7.8Hz) 1.95-2.15(2H, m) 1.00-1.75(13H, m) 1.36(9H, s) 0.85(6H, d, J=6.6Hz)
76		77 - 78	8.57(1H, d, J=2.7Hz) 8.06(1H, brs) 7.27(1H, d, J=7.8Hz) 7.08(1H, dd, J=2.7, 7.8Hz) 1.95-2.10(2H, m) 1.05-1.65(13H, m) 1.34(9H, s) 0.84(6H, d, J=6.6Hz)
77		80 - 82	8.38(1H, d, J=8.7Hz) 7.99(1H, brs) 7.40(1H, dd, J=2.7, 8.7Hz) 7.35(1H, d, J=2.7Hz) 1.90-2.05(2H, m) 1.05-1.65(13H, m) 1.35(9H, s) 0.84(6H, d, J=6.6Hz)

Table 30

Example	Compound	m.p. (℃)	^{1}H NMR ($CDCl_3$ 300MHz)
78		76 - 77	8.20(1H, d, J=2.7Hz) 8.09(1H, brs) 7.22(1H, d, J=8.4Hz) 6.66(1H, dd, J=2.7, 8.4Hz) 3.85(3H, s) 1.95-2.05(2H, m) 1.05-1.65(13H, m) 1.34(9H, s) 0.84(6H, d, J=6.6Hz)
79		55 - 56	8.34(1H, dd, J=3.0, 11.4Hz) 8.11(1H, brs) 7.31(1H, dd, J=6.3, 8.4Hz) 6.81(1H, ddd, J=3.0, 8.4, 11.4Hz) 1.95-2.15(2H, m) 1.05-1.65(13H, m) 1.34(9H, s) 0.84(6H, d, J=6.6Hz)
80		97 - 98	8.44(1H, dd, J=8.1, 12.9Hz) 7.98(1H, brs) 7.19(1H, dd, J=8.4, 9.6Hz) 1.95-2.05(2H, m) 1.05-1.65(13H, m) 11.34(9H, s) 0.84(6H, d, J=6.6Hz)
81		94 - 95	8.29-8.35(1H, m) 7.90(1H, brs) 7.09-7.19(2H, m) 1.92-2.06(2H, m) 1.09-1.55(13H, m) 1.35(9H, s) 0.85(6H, d, J=6.6Hz)

[0137] The compounds 66-1 through 66-53 shown in Tables 31 through 35 were also obtained in the same manner as in Example 66.

Table 31

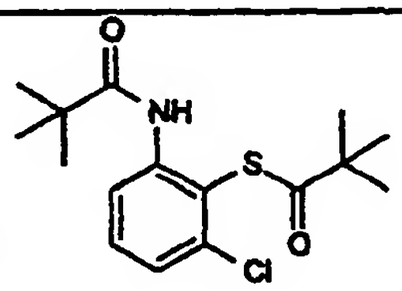
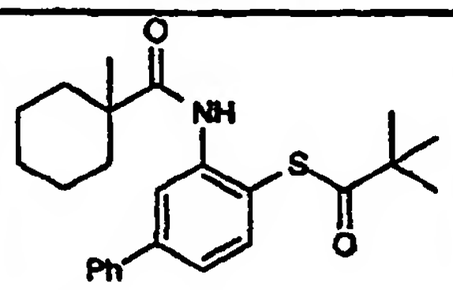
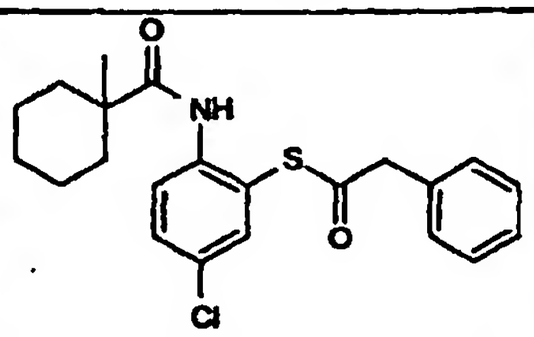
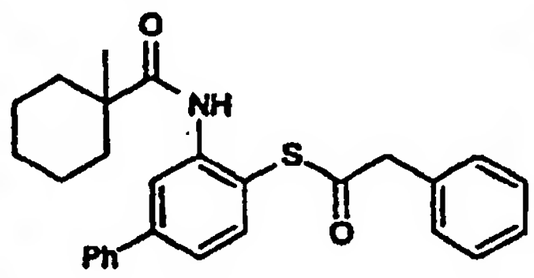
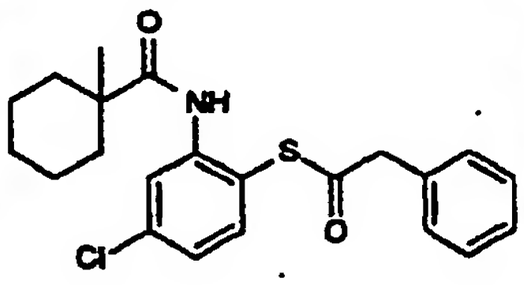
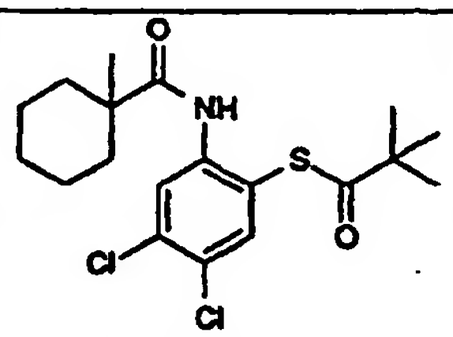
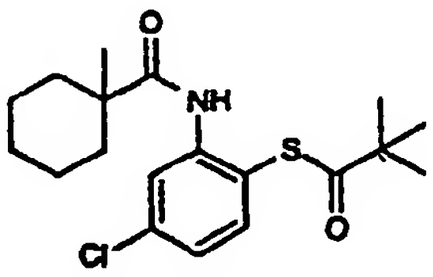
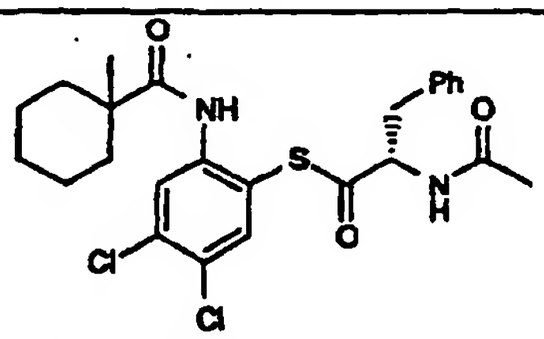
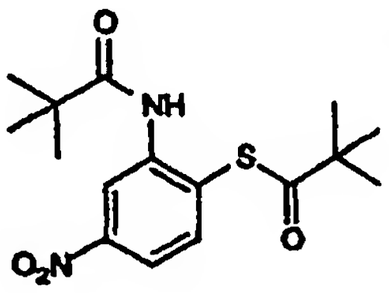
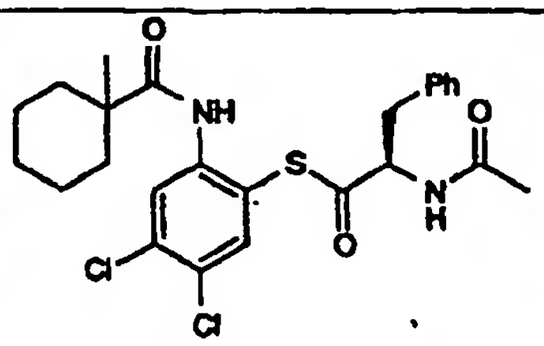
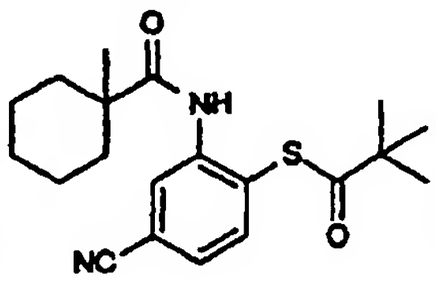
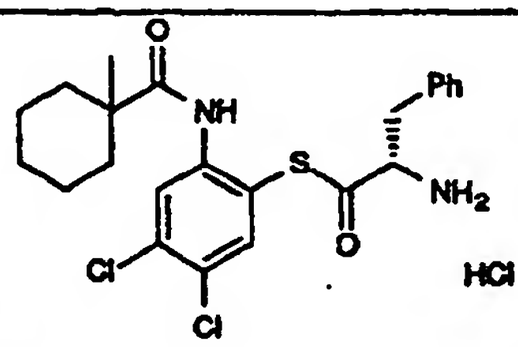
No.	Compound	No.	Compound
66-1		66-7	
66-2		66-8	
66-3		66-9	
66-4		66-10	
66-5		66-11	
66-6		66-12	

Table 32

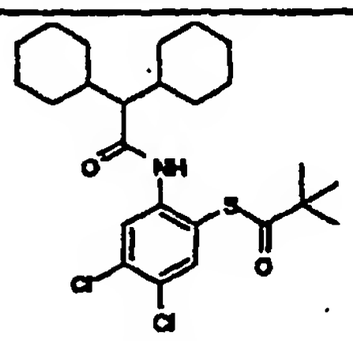
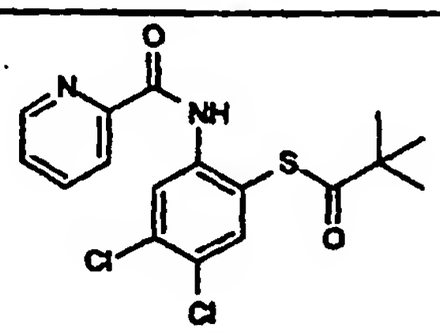
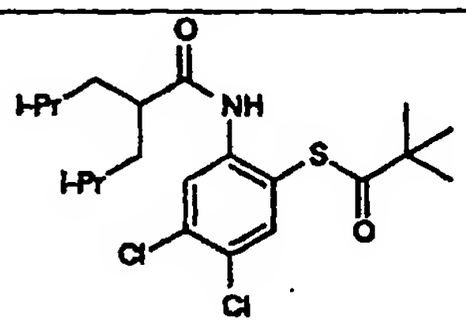
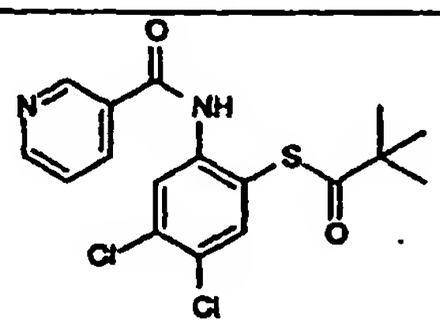
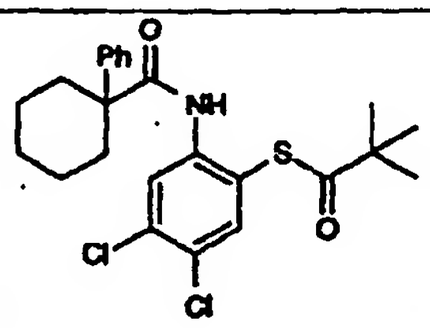
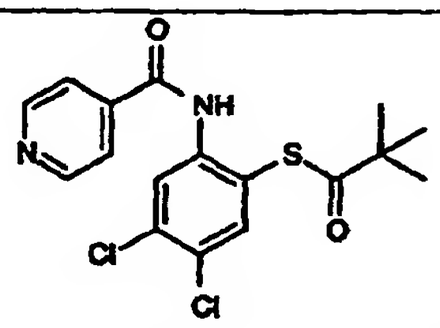
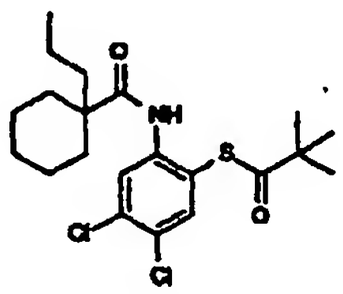
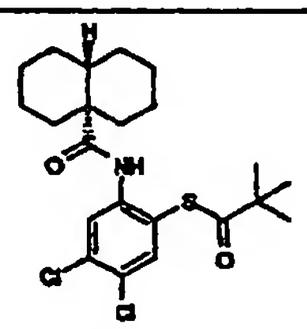
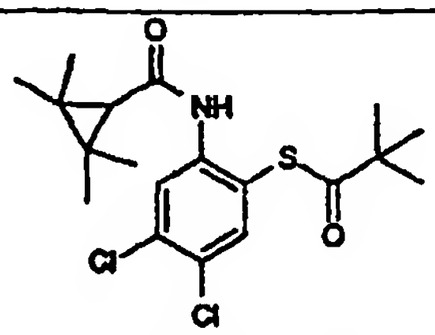
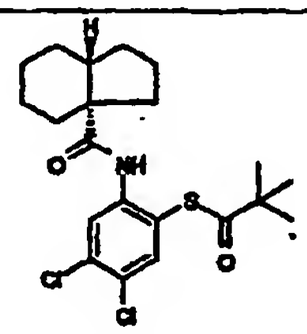
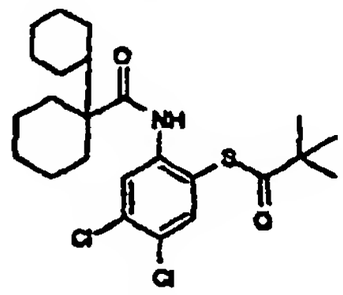
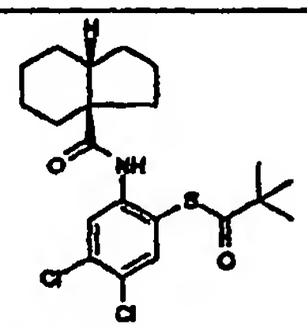
No.	Compound	No.	Compound
66-13		66-19	
66-14		66-20	
66-15		66-21	
66-16		66-22	
66-17		66-23	
66-18		66-24	

Table 33

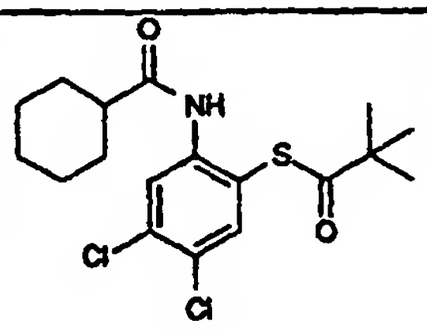
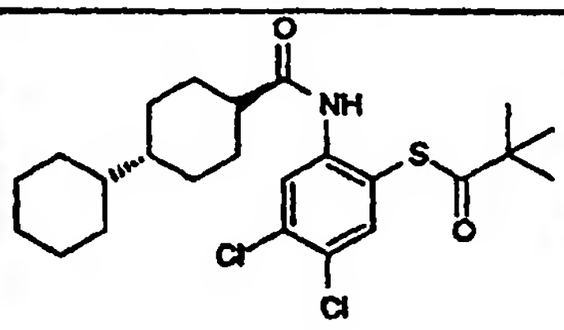
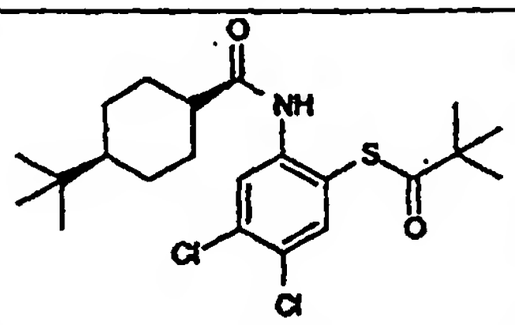
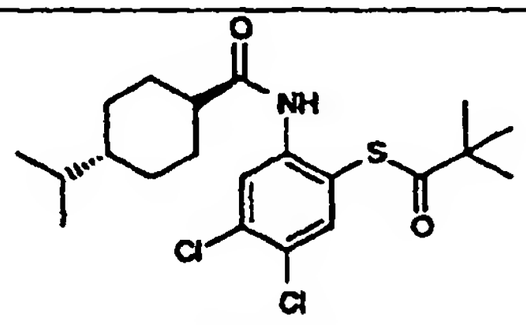
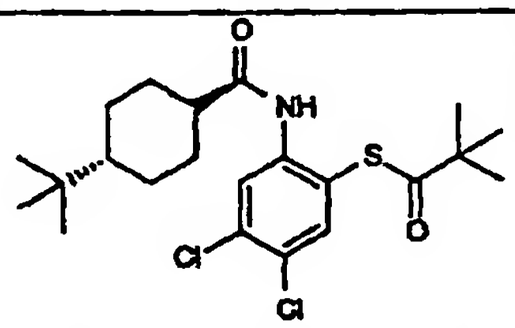
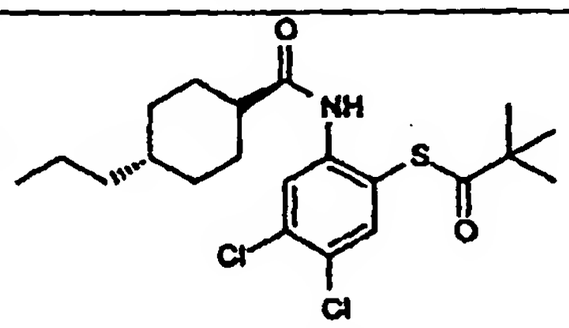
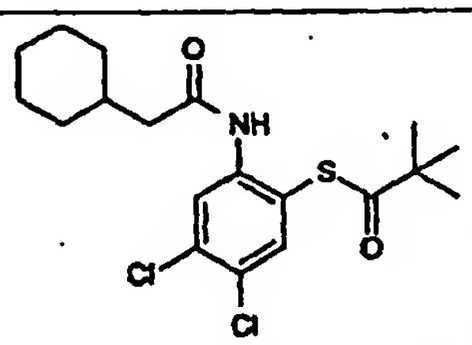
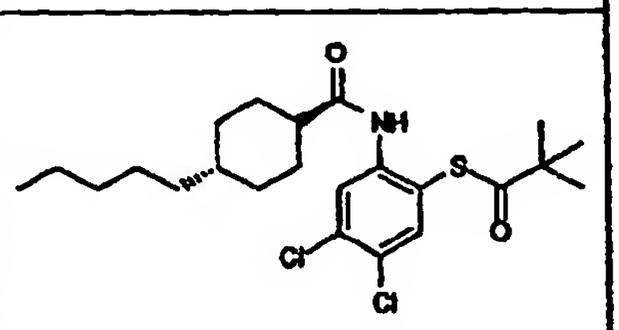
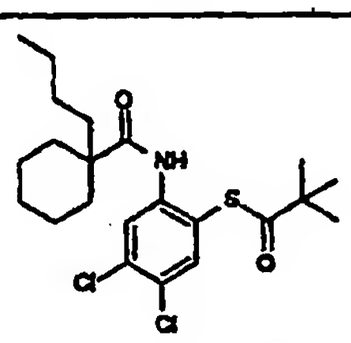
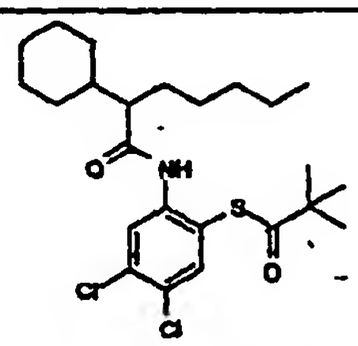
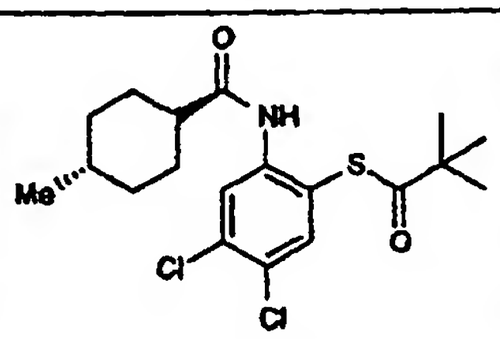
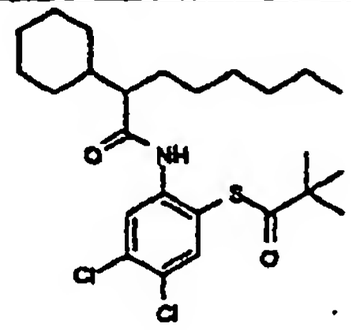
No.	Compound	No.	Compound
66-25		66-31	
66-26		66-32	
66-27		66-33	
66-28		66-34	
66-29		66-35	
66-30		66-36	

Table 34

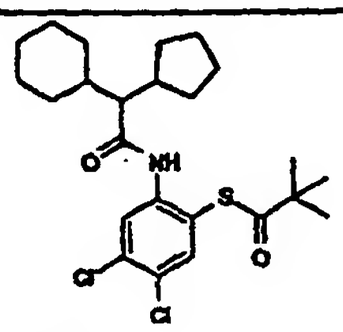
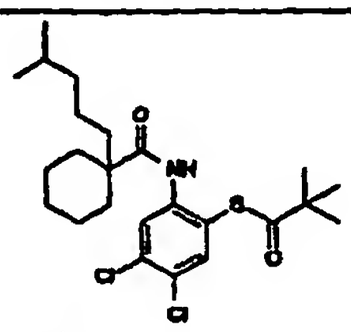
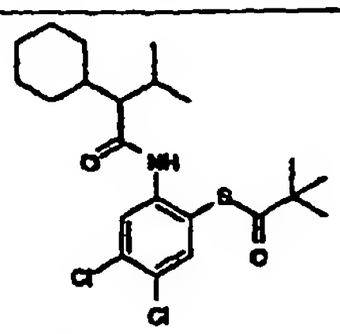
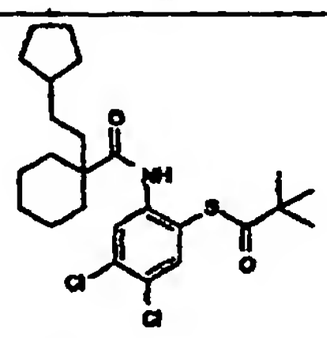
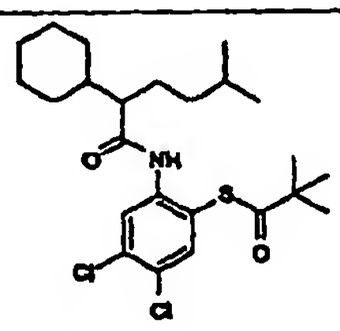
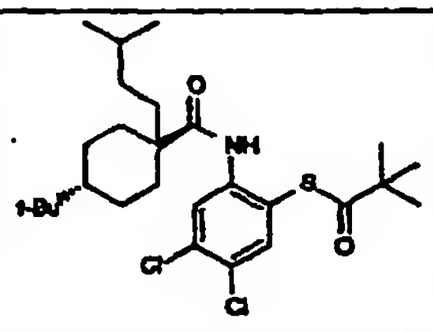
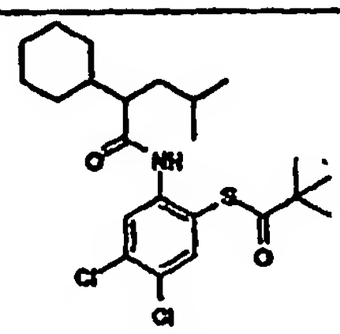
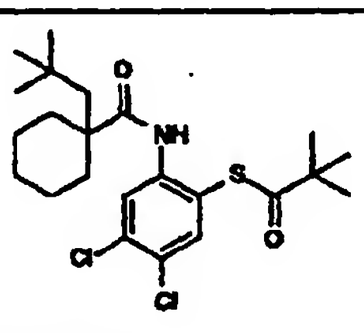
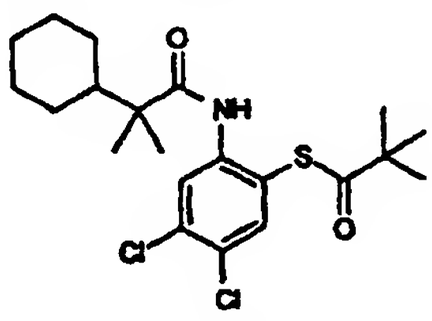
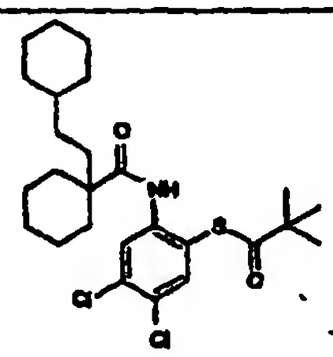
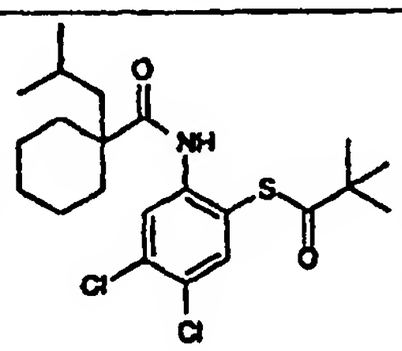
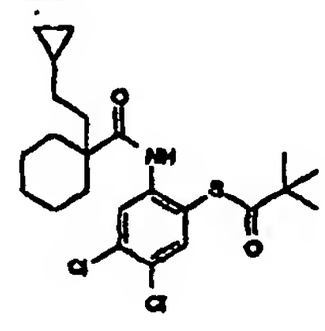
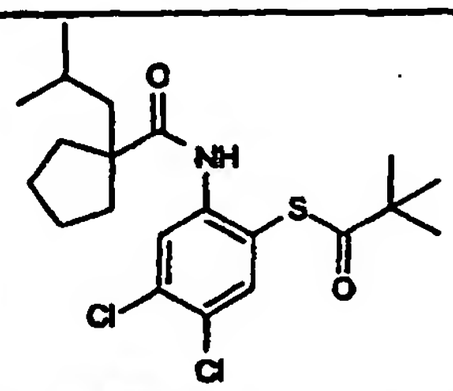
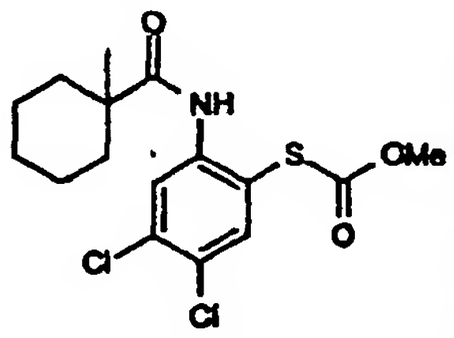
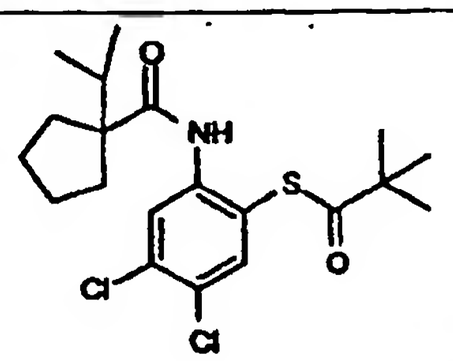
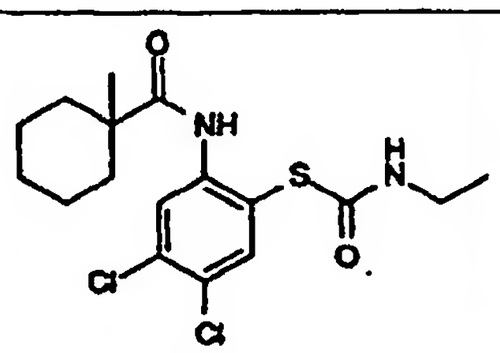
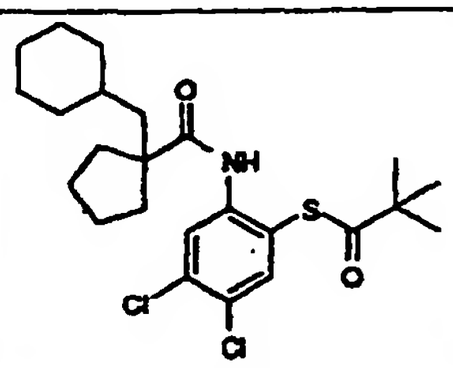
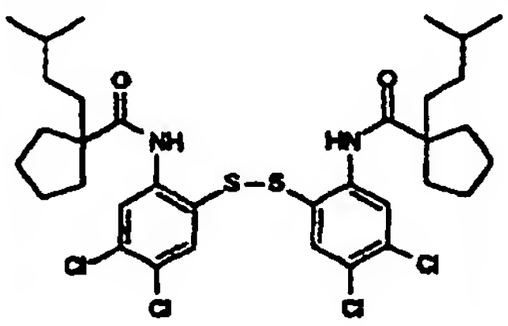
No.	Compound	No.	Compound
66-37		66-43	
66-38		66-44	
66-39		66-45	
66-40		66-46	
66-41		66-47	
66-42		66-48	

Table 35

No.	Compound	No.	Compound
66-49		66-52	
66-50		66-53	
66-51		82-1	

Example 82

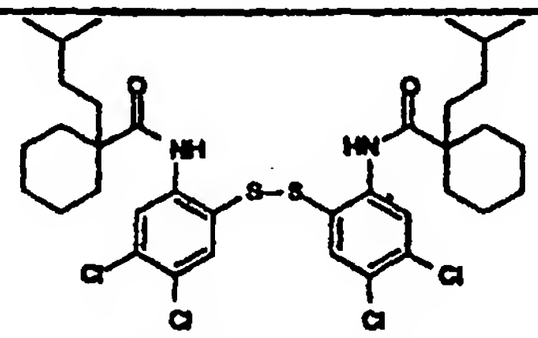
Synthesis of bis-[4,5-dichloro-2-(1-isopentylcyclohexanecarbonylamino)phenyl] disulfide (formula (I); R=1-isopentylcyclohexyl, X_1, X_4 =a hydrogen atom, X_2, X_3 =a chlorine atom, Y=carbonyl, Z=4,5-dichloro-2-(1-isopentylcyclohexanecarbonylamino)phenylthio)

Step 10) N-(4,5-dichloro-2-mercaptophenyl)-1-isopentylcyclohexanecarboxamide (formula (III-2); R=1-isopentylcyclohexyl, X_1, X_4 =a hydrogen atom, X_2, X_3=a chlorine atom, Y=carbonyl)

[0138] A tetrahydrofuran (2 ml)-methanol (1 ml) solution containing S-[4,5-dichloro-2-(1-isopentylcyclohexanecarbonylamino)phenyl] N,N-dimethylthiocarbamate (400 mg) obtained in the same manner as in step 9 of Example 19 and potassium hydroxide (180 mg) was refluxed for 2 hours under heating and the resulting mixture was allowed to cool. After adding water thereto, the aqueous layer was washed with hexane, was acidified with a saturated aqueous potassium hydrogensulfate, and was extracted with chloroform. The organic layer was washed with water and a saturated brine, and dried over anhydrous sodium sulfate.
After removing anhydrous sodium sulfate by filtration, the organic solvent was distilled off under reduced pressure to obtain the crude compound.

[0139] Step 3) A dimethyl sulfoxide solution (5 ml) of the crude product obtained in the above step 10) was stirred for 2 hours at 130°C and the mixture was allowed to cool. Water was added to the solution, which was extracted with chloroform. The organic layer was washed with water and saturated brine, and dried over anhydrous sodium sulfate. The residue obtained after concentration was purified by silica gel column chromatography (a developing solvent; hexane : ethyl acetate=30:1) to obtain the compound (200 mg, yield: 60%).

Table 36

Example	Compound	m.p. (℃)	^{1}H NMR ($CDCl_3$ 300MHz)
8 2		Amorphous	8.78(2H, s) 8.38(2H, brs) 7.24(2H, s) 1.80-2.00(4H, m) 1.00-1.75(26, m) 0.86(12H, d, J=6.6Hz)

[0140] The compound 82-1 shown in Table 35 was obtained in the same manner as in Example 82.

Example 83

Synthesis of 2-tetrahydrofurylmethyl 2-(1-isopentylcyclohexanecarbonylamino)phenyl disulfide (formula (I); R=1-isopentylcyclohexyl, X_1, X_2, X_3, X_4=a hydrogen atom, Y=carbonyl, Z=2-tetrahydrofurfurylmethylthio)

[0141] Step 5) An ethanol (6 ml)-water (6 ml) solution containing tetrahydrofurfuryl chloride (3.0g) and sodium thiosulfate (4.13 g) was refluxed for 17 hours under heating and the mixture was allowed to cool. Ethanol was removed under reduced pressure and an aqueous solution of Bunte salt was obtained. An aqueous solution (1 ml) of N-(2-mercaptophenyl)-1-isopentylcyclohexanecarboxamide (380 mg) obtained as in Example 11 and sodium hydroxide (50 mg) was added dropwise to the solution at 0°C and the solution was stirred for 1.5 hour. After addition of ether, the organic layer was successively washed with an aqueous sodium hydroxide, water, and a saturated brine, and dried over anhydrous sodium sulfate. The residue obtained by concentration under reduced pressure was purified by silica gel column chromatography (a developing solvent: hexane : ethyl acetate=8:1) to obtain the desired compound (128 mg, yield: 24 %).

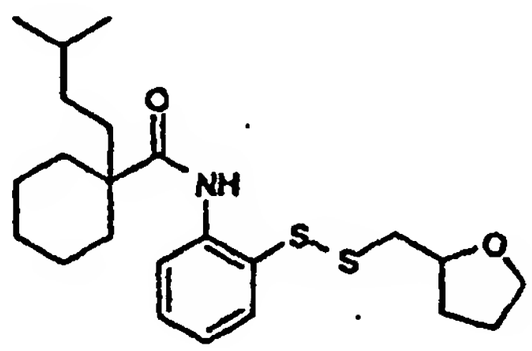
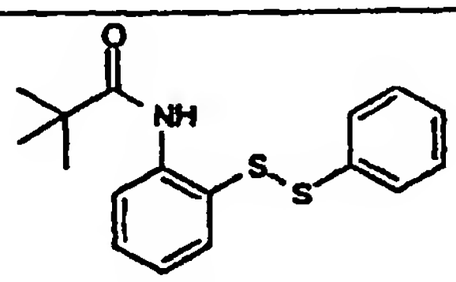
Example 84

Synthesis of phenyl 2-pivaloylaminophenyl disulfide (formula (I); R=t-butyl, X_1, X_2, X_3, X_4, =a hydrogen atom, Y=carbonyl, Z=phenylthio)

[0142] Step 5') Trimethylsilane-imidazole (202 mg) was added to a carbon tetrachloride solution (5 ml) containing thiophenol (159 mg). The solution was stirred for 2 hours at room temperature. The deposited imidazole was filtered off to obtain a solution.

[0143] Then, sulfuryl chloride (97 mg) and triethylamine (1 drop) were successively added to a carbon tetrachloride solution (5 ml) containing bis-[2-(pivaloylamino)phenyl] disulfide (300 mg) obtained as in the step 1 of Example 1 at 0°C. The solution was stirred for 1.5 hour at the same temperature and was added dropwise to the above solution cooled in an ice-salt bath and the mixture was continuously stirred for 2.5 hour. After completion of the reaction, water was added and the solution was extracted with chloroform. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the resulting residue was purified by silica gel column chromatography (a developing solvent; hexane : ethyl acetate=12:1) to obtain the desired compound (337 mg, yield: 74%).

Table 37

Example	Compound	m.p. (℃)	^{1}H NMR ($CDCl_3$ 300MHz)
83		Oil	8.53(1H, brs) 8.44(1H, dd, J=1.5, 8.4Hz) 7.58(1H, dd, J=1.5, 7.8Hz) 7.40(1H, ddd, J=1.5, 7.8, 8.4Hz) 7.04(1H, dt, J=1.5, 7.8Hz) 4.14(2H, quint, J=6.6Hz) 3.86(1H, dt, J=8.4, 6.6Hz) 3.77(1H, dt, J=8.4, 6.6Hz) 2.96(1H, dd, J=6.6, 13.2Hz) 2.84(1H, dd, J=6.6, 13.2Hz) 1.80-2.20(5H, m) 1.10-1.75(14H, m) 0.86(6H, d, J=6.6Hz)
84		Oil	8.51(1H, brs) 8.40(1H, dd, J=1.5,8.4Hz) 7.20-7.50(7H, m) 6.97(1H, dt, J=1.5, 7.8Hz) 1.30(9H, s)

[0144] In the following, the results of the test for the CETP activity inhibitory effect of the compounds of the present invention are shown.

[Test Examples]

(1) Preparation of donor lipoprotein

[0145] Potassium bromide (KBr) was added to the plasma of healthy subjects (40 ml) to adjust specific gravity to d=1.125 g/ml. Density gradient centrifugation (227,000 x g, 4°C, 17 hours) was conducted to obtain a fraction with specific gravity d>1.125 g/ml (HDL, fraction). The fraction thus obtained was dialyzed against a PBS solution [10 mM Na_2HPO_4/10 mM NaH_2PO_4/0.15 M NaCl/1 mM EDTA (pH 7.4)]. Then, tritium-labeled cholesterol (10 nM) (50.3 Ci/mM) was dissolved in 95 % ethanol and added gradually to the above HDL_3 fraction under stirring. The solution was incubated for 18 hours at 37°C [Tritium-labeled cholesterol was esterified by this procedure by the action of lecithin:cholesterol acyltransferase (LCAT) present on the surface of HDL_3 and taken up into the interior of HDL_3 as tritium-labeled cholesterylester ([^{3}H]CE)]. After, incubation, KBr was added and specific gravity was adjusted to d=1.21 g/ml. Density gradient centrifugation (227,000 x g, 4°C, 17 hours) was conducted and the fraction with d<1.21 g/ml was harvested. The fraction thus obtained was dialyzed against the above PBS solution to obtain HDL_3 that took up [^{3}H] CE ([^{3}H]CE-HDL_3, specific gravity: 1.125< d <1.21, specific activity: 101,000 dpm/nM), which served as donor lipoprotein.

(2) Preparation of acceptor lipoprotein

[0146] Physiological saline (specific gravity d=1.006 g/ml) was layered upon the plasma of healthy subjects (100 ml). Density gradient centrifugation (227,000 x g, 4°C, 4 hours) was conducted and the fraction with specific gravity d>1.006 g/ml was harvested. KBr was added to the fraction thus obtained to adjust specific gravity to d=1.063 g/ml and density gradient centrifugation (227,000 x g, 4°C, 20 hours) was conducted to harvest the fraction with specific gravity d>1.063 g/ml. The thus-obtained fraction was dialyzed against the above PBS solution to obtain fractions containing IDL and LDL (specific gravity: 1.006< d <1.063), which served as acceptor lipoprotein.

Test example 1: *in vitro* CETP activity inhibitory effect in whole plasma

[0147] Plasma containing [^{3}H] CE-HDL_3 (600,000 dpm/ml) was prepared by adding donor lipoprotein obtained in the above (1) to plasma from healthy subjects. A sample solution was prepared using a 1:1 solution of N-methylpyrrolidone and polyethyleneglycol 400 as a solvent. The sample solution or the solvent alone (2 µl) and the plasma containing [^{3}H]CE-HDL_3 (100 µl) were added to microtubes and incubated for 4 hours at 3°C or 4°C. After ice cooling, a TBS solution (20 mM Tris/0.15 M NaCl (pH 7.4)] containing 0.15 M magnesium chloride and 0.3 % dextran sulfate (100 µl) were added to each microtube and mixed well. After allowing the microtubes to stand at 4°C for 30 minutes, centrifugation (8,000 rpm, 4°C, 10 minutes) was conducted and the radioactivity of the resulting supernatant (HDL fraction) was determined with a scintillation counter. The difference between the values obtained after incubation at 4°C and 37°C with the solvent alone was regarded as CETP activity and a decrease (%) of the measured values produced by the samples was regarded as inhibition rate (%) of CETP activity. Based on the inhibition rate (%) of CETP activity, IC_{50} value of each sample was calculated.

[0148] The results are shown in Tables 38-48.

Test Example 2: *ex vivo* CETP activity inhibitory effect of plasma from transgenic mice

[0149] Samples were suspended in a 0.5 % methylcellulose solution and administered orally using a plastic probe to transgenic mice having introduced human CETP gene (hereafter referred to as mice; prepared using the method described in Japanese Patent Application No. Hei 8-130660), which had been fasted overnight. Blood was collected before administration, and 6 hours after administration CETP activity in the plasma was determined using the following method.

[0150] Donor lipoprotein ([^{3}H]CE-HDL_3, containing 0.21 µg cholesterol) obtained in the above (1), acceptor lipoprotein obtained in the above (2) (containing 21 µg of cholesterol), and 0.9 µl of mice plasma were added to microtubes. A total volume was adjusted to 600 µl/tube with a TBS solution [10 mM Tris/0.15 M NaCl (pH 7.4)]. The microtubes were incubated for 15 hours at 37°C or 4°C. Then, an ice-cooled TBS solution (400 µl/tube) and a 0.3 % dextran sulfate solution (100 µl/tube) containing 0.15 M magnesium chloride were added to the microtubes and mixed well. After allowing the microtubes to stand for 30 minutes at 4°C, centrifugation (8,000 rpm, 4°C, 10 minutes) was carried out and radioactivity of the resulting supernatant (HDL fraction) was determined with a scintillation counter. The difference between measured values obtained by incubating plasma of individual mice at 4°C and 37°C before administration of the samples were regarded as CETP activity and a decrease (%) of measured values after administration of samples was regarded as inhibition rate (%) of CETP activity.

[0151] The results are shown in Tables 38-48.

Table 38

Example	CETP activity inhibition in whole plasma IC_{50}(µM)	CETP activity inhibitory rate in plasma from transgenic mouse(%)			
		10mg/kg,p.o.	30mg/kg,p.o.	100mg/kg,p.o.	300mg/kg,p.o.
1	20				
3	101				
4	175				
5	3				
6	5				
7	2				
8	3			25	
9	99				
11	5	27	45	57	
12	17				
13	5				

Table 38 (continued)

Example	CETP activity inhibition in whole plasma $IC_{50}(\mu M)$	CETP activity inhibitory rate in plasma from transgenic mouse(%)			
		10mg/kg,p.o.	30mg/kg,p.o.	100mg/kg,p.o.	300mg/kg,p.o.
14	8		9		
15	12				
16	8				
17	8				
18	6				
19	179				
20	16				
21	9				
22	56	22	44		

Table 39

Example	CETP activity inhibition in whole plasma $IC_{50}(\mu M)$	CETP activity inhibitory rate in plasma from transgenic mouse(%)			
		10mg/kg,p.o.	30mg/kg,p.o.	100mg/kg,p.o.	300mg/kg,p.o.
23			18		
24	29		29		
25	11	19	45	52	
26	7		44		
27	7		31		
28	6		36		
30	72				
31	32				
32	32				
33	61	23	39	52	55
34	9		4		
35	4				
36	16		19		
37	7	18	42	47	
38	6	15	40		
39	11	17	41		
40	23	20	48	64	
41	7	27	42		
42	9	31	38		
43	49				

Table 40

Example	CETP activity inhibition in whole plasma $IC_{50}(\mu M)$	CETP activity inhibitory rate in plasma from transgenic mouse(%)			
		10mg/kg,p.o.	30mg/kg,p.o.	100mg/kg,p.o.	300mg/kg,p.o.
44	23				
45	7	18	36		
46	5	22	48		
47	6		31		
48	49		31	50	
49	6		29		
50	2				
51	16				
52	8		8		
53	8				
54	12				
55	65				
56	13		34		
57	41				
59	4		44		
60	41		44		
61	4		38		
62	4		38		
63	4		43		
64	4		34		

Table 41

Example	CETP activity inhibition in whole plasma $IC_{50}(\mu M)$	CETP activity inhibitory rate in plasma from transgenic mouse(%)			
		10mg/kg,p.o.	30mg/kg,p.o.	100mg/kg,p.o.	300mg/kg,p.o.
66	7				
67	9				
68	10				
69	6				
70	4				
71	4				
72	74				

Table 41 (continued)

Example	CETP activity inhibition in whole plasma IC_{50}(μM)	CETP activity inhibitory rate in plasma from transgenic mouse(%)			
		10mg/kg,p.o.	30mg/kg,p.o.	100mg/kg,p.o.	300mg/kg,p.o.
73	37				
74	14		5		
75	25		1		
76	18		4		
77	17		1		
78			11		
79	60	14	26		
80	6		12		
81	21		10		
82	7				
83	5				
84	158				

Table 42

No.	CETP activity inhibition in whole plasma IC_{50} (μM)	CETP activity inhibitory rate in plasma from transgenic mouse(%)			
		10mg/kg,p.o.	30mg/kg,p.o.	100mg/kg,p.o.	300mg/kg,p.o.
1-1	41				
1-2	25				
1-6	22				
1-7	24				
1-8	21				
1-12	12				
1-13	18				
19-1	19				
19-2	33				
19-5	17				
19-6	18				
25-4	32				
25-7	46				
25-8	25				
25-12	33				
25-13	28				

Table 42 (continued)

No.	CETP activity inhibition in whole plasma IC_{50} (μM)	CETP activity inhibitory rate in plasma from transgenic mouse(%)			
		10mg/kg,p.o.	30mg/kg,p.o.	100mg/kg,p.o.	300mg/kg,p.o.
25-14	30				
25-16	41				
25-17	23				
25-18	19				

Table 43

No.	CETP activity inhibition in whole plasma IC_{50}(μM)	CETP activity inhibitory rate in plasma from transgenic mouse(%)			
		10mg/kg,p.o.	30mg/kg,p.o.	100mg/kg,p.o.	300mg/kg,p.o.
25-19	22				
25-20	48				
25-21	28				
25-22	27				
25-23	25				
25-25	24				
25-26	22				
25-27	21				
25-28	21				
25-30	21				
25-31	21				
25-32	20				
25-33	18				
25-34	21				
25-35	27				
25-36	30				
25-37	24				
25-38	20				
25-39	22				
25-40	23				

Table 44

No.	CETP activity inhibition in whole plasma $IC_{50}(\mu M)$	CETP activity inhibitory rate in plasma from transgenic mouse(%)			
		10mg/kg,p.o.	30mg/kg,p.o.	100mg/kg,p.o.	300mg/kg,p.o.
25-41	26				
25-42	22				
25-44	9				
25-45	13		21		
25-46	9			35	
25-47	29				
25-48	23				
25-49	21		16		
25-52	68	19	40		
25-53	7		26		
25-54	6				
25-55	10				
25-56	7		24		
25-57	7	18	46		
25-59	8	20	37		
25-60	5				
25-61	5		28		
25-63	21			25	
25-64	20				
25-65	9				

Table 45

No.	CETP activity inhibition in whole plasma $IC_{50}(\mu M)$	CETP activity inhibitory rate in plasma from transgenic mouse(%)			
		10mg/kg,p.o.	30mg/kg,p.o.	100mg/kg,p.o.	300mg/kg,p.o.
25-66	35				
25-67	40				
25-72	27				
25-76	36				
25-77	7				
25-78	11				
25-79	6				

Table 45 (continued)

No.	CETP activity inhibition in whole plasma $IC_{50}(\mu M)$	CETP activity inhibitory rate in plasma from transgenic mouse(%)			
		10mg/kg,p.o.	30mg/kg,p.o.	100mg/kg,p.o.	300mg/kg,p.o.
25-80	5				
25-81	14				
25-82	17				
25-83	18				
25-84	10			17	
25-85	7				
25-86	10				
25-87	6				
25-91	22				
25-92	19				
25-93	22				
25-94	18				
25-95	18				

Table 46

No.	CETP activity inhibition in whole plasma $IC_{50}(\mu M)$	CETP activity inhibitory rate in plasma from transgenic mouse(%)			
		10mg/kg,p.o.	30mg/kg,p.o.	100mg/kg,p.o.	300mg/kg,p.o.
25-96	8				
25-97	9			19	
25-98	8				
25-99	6				
25-100	16		25		
25-101	7		8		
25-102	8			9	
25-103	12				
25-104	9				
25-105	6			14	
25-106	10		29		
25-107	11		22		
25-108	7			8	
66-3	24				
66-4	28				
66-9	9				

Table 46 (continued)

No.	CETP activity inhibition in whole plasma $IC_{50}(\mu M)$	CETP activity inhibitory rate in plasma from transgenic mouse(%)			
		10mg/kg,p.o.	30mg/kg,p.o.	100mg/kg,p.o.	300mg/kg,p.o.
66-10	23				
66-11	22				
66-12	17				
66-14	11				

Table 47

No.	CETP activity inhibition in whole plasma $IC_{50}(\mu M)$	CETP activity inhibitory rate in plasma from transgenic mouse (%)			
		10mg/kg,p.o.	30mg/kg,p.o.	100mg/kg,p.o.	300mg/kg,p.o.
66-16	8				
66-17	18				
66-18	11				
66-21	41				
66-22	19				
66-23	13				
66-24	12				
66-25	19				
66-26	8				
66-27	9				
66-28	18				
66-29	7				
66-30	19				
66-31	27				
66-32	22				
66-33	19				
66-34	22				
66-38	26				
66-40	42				
66-41	25				

Table 48

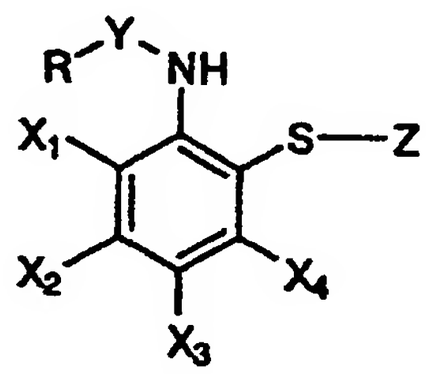
No.	CETP activity inhibition in whole plasma $IC_{50}(\mu M)$	CETP activity inhibitory rate in plasma from transgenic mouse (%)			
		10mg/kg,p.o.	30mg/kg,p.o.	100mg/kg,p.o.	300mg/kg,p.o.
66-42	10				
66-43	23				
66-46	35				
66-48	11				
66-49	40				
66-51	45				
66-52	46				
66-53	15				
82-1	5				

Industrial Applicability

[0152] The above test results reveal that the compounds (I) of the present invention have an excellent CETP activity inhibitory effect. Thus, the compounds can reduce IDL, VLDL, and LDL, which aggravate atherosclerosis, and increase HDL that acts inhibitory thereto, and, therefore, are useful as a conventionally unknown, new type of a preventive or therapeutic agent for hyperlipidemia. The compound is also useful as a preventive or therapeutic agent for atherosclerotic diseases.

Claims

1. A CETP activity inhibitor comprising as an active ingredient a compound represented by formula (I):



(I)

wherein

R represents

a straight chain or branched C_{1-10} alkyl group;
a straight chain or branched C_{2-10} alkenyl group;
a halo-C_{1-4} lower alkyl group;
a substituted or unsubstituted C_{3-10} cycloalkyl group;
a substituted or unsubstituted C_{5-8} cycloalkenyl group;
a substituted or unsubstituted C_{3-10} cycloalkyl C_{1-10} alkyl group;
a substituted or unsubstituted aryl group;
a substituted or unsubstituted aralkyl group; or
a substituted or unsubstituted 5- or 6-membered heterocyclic group having 1-3 nitrogen, oxygen, or sulfur atoms,

X_1, X_2, X_3, and X_4 may be the same or different and represents

a hydrogen atom;
a halogen atom;
a C_{1-4} lower alkyl group;
a halo-C_{1-4} lower alkyl group;
a C_{1-4} lower alkoxy group;
a cyano group;
a nitro group;
an acyl group; or
an aryl group,

Y represents

-CO-; or
-SO_2, and

Z represents

a hydrogen atom; or
a mercapto-protecting group,
a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

2. The CETP activity inhibitor comprising as an active ingredient the compound as claimed in claim 1, wherein

R represents

a straight chain or branched C_{1-10} alkyl group;
a straight chain or branched C_{2-10} alkenyl group;
a halo-C_{1-4} lower alkyl group substituted with 1-3 halogen atoms selected from fluorine, chlorine, and bromine;
a C_{3-10} cycloalkyl group, a C_{5-8} cycloalkenyl group, or a C_{3-10} cycloalkyl C_{1-10} alkyl group, each of which may have 1-4 substituents selected from the group consisting of

a straight chain or branched C_{1-10} alkyl group,
a straight chain or branched C_{2-10} alkenyl group,
a C_{3-10} cycloalkyl group,
a C_{5-8} cycloalkenyl group,
a C_{3-10} cycloalkyl C_{1-10} alkyl group,
an aryl group selected from phenyl, biphenyl, and naphthyl,
an oxo group, and
an aralkyl group having an aryl group selected from phenyl, biphenyl, and naphthyl; or
an aryl, aralkyl, or 5- or 6-membered heterocyclic group with 1-3 nitrogen, oxygen or sulfur atoms, each of which may have 1-4 substituents selected from the group consisting of

a straight chain or branched C_{1-10} alkyl group,
a straight chain or branched C_{2-10} alkenyl group,
a halogen atom selected from fluorine, chlorine, and bromine,
a nitro group, and
a halo-C_{1-4} lower alkyl group having a halogen atom selected from fluorine, chlorine, and bromine;

Z represents

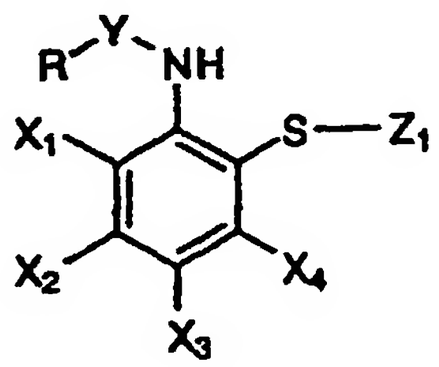
a hydrogen atom;
a mercapto-protecting group selected from the group consisting of

a C_{1-4} lower alkoxymethyl group,

a C_{1-4} lower alkylthiomethyl group,
an aralkyloxymethyl group having an aryl group selected from phenyl, biphenyl, and naphthyl,
an aralkylthiomethyl group having an aryl group selected from phenyl, biphenyl, and naphthyl,
a C_{3-10} cycloalkyloxymethyl group,
a C_{5-8} cycloalkenyloxymethyl group,
a C_{3-10} cycloalkyl C_{1-10} alkoxymethyl group,
an aryloxymethyl group having an aryl group selected from phenyl, biphenyl, and naphthyl,
an arylthiomethyl group having an aryl group selected from phenyl, biphenyl, and naphthyl,
an acyl group,
an acyloxy group,
an aminocarbonyloxymethyl group,
a thiocarbonyl group, and
a thio group,

a prodrug compound thereof, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

3. The CETP activity inhibitor comprising as an active ingredient the compound as claimed in claim 2, which is represented by the formula (I-1):

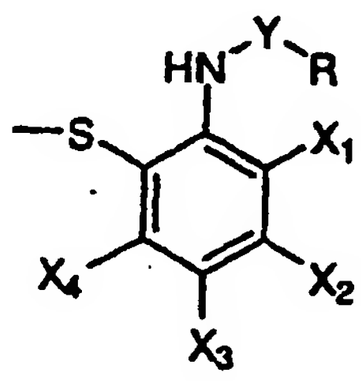


(I-1)

wherein R, X_1, X_2, X_3, X_4, and Y are the same as in claim 2 and

Z_1 represents

a hydrogen atom;
a group represented by the formula



wherein R, X_1, X_2, X_3, X_4, and Y are the same as described above;

$-Y_1R_1$,

wherein Y_1 represents -CO-; or
-CS-, and

R_1 represents

a substituted or unsubstituted straight chain or branched C_{1-10} alkyl group;
a C_{1-4} lower alkoxy group;

a C_{1-4} lower alkylthio group;
a substituted or unsubstituted amino group;
a substituted or unsubstituted ureido group;
a substituted or unsubstituted C_{3-10} cycloalkyl group;
a substituted or unsubstituted C_{3-10} cycloalkyl C_{1-10} alkyl group;
a substituted or unsubstituted aryl group;
a substituted or unsubstituted aralkyl group;
a substituted or unsubstituted arylalkenyl group;
a substituted or unsubstituted arylthio group;
a substituted or unsubstituted 5- or 6-membered heterocyclic group having 1-3 nitrogen, oxygen, or sulfur atoms; or
a substituted or unsubstituted 5- or 6-membered heteroarylalkyl group; or

$$-S-R_2,$$

wherein R_2 represents
a substituted or unsubstituted C_{1-4} lower alkyl group; or
a substituted or unsubstituted aryl group,
a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

4. The CETP activity inhibitor comprising as an active ingredient the compound as claimed in claim 3, wherein

R_1 represents

a straight chain or branched C_{1-10} alkyl group which may have 1-3 substituents selected from the group consisting of

a halogen atom selected from fluorine, chlorine, and bromine,
a C_{1-4} lower alkoxy group,
an amino group that may be substituted with a C_{1-4} lower alkyl, acyl, or hydroxyl group,
a C_{1-4} lower alkylthio group,
a carbamoyl group,
a hydroxyl group,
an acyl group,
an acyloxy group having an acyl group,
a carboxyl group, and
an aryloxy group that may be substituted with a halogen atom selected from fluorine, chlorine, and bromine;

a C_{1-4} lower alkoxy group;
a C_{1-4} lower alkylthio group;
an amino or ureido group that may have 1-2 substituents selected from the group consisting of
a C_{1-4} lower alkyl group,
a hydroxyl group,
an acyl group, and
an aryl group that may be substituted with a lower C_{1-4} alkoxy group;

a C_{3-10} cycloalkyl or C_{3-10} cycloalkyl C_{1-10} alkyl group that may have substituents selected from the group consisting of

a straight or branched C_{1-10} alkyl group,
a C_{3-10} cycloalkyl group,
a C_{5-8} cycloalkenyl group,
an aryl group,
an amino group,
a C_{1-4} lower alkylamino group having a C_{1-4} lower alkyl group, and
an acylamino group having an acyl group;

an aryl group, an aralkyl group, an arylalkenyl group, or an arylthio group, each of which may have 1-4 substituents selected from the group consisting of

a C_{1-10} alkyl group,
a halogen atom selected from fluorine, chlorine, and bromine,
a nitro group,
a hydroxyl group,
a C_{1-4} lower alkoxy group,
a C_{1-4} lower alkylthio group,
an acyl group,
a halo-C_{1-4} lower alkyl group having a halogen atom selected from fluorine, chlorine, and bromine, and
an amino group that may be substituted with a C_{1-4} lower alkyl or acyl group;

a 5- or 6-membered heterocyclic group having 1-3 nitrogen, oxygen or sulfur atoms or a 5- or 6-membered heteroarylalkyl group that may have 1-4 substituents selected from the group consisting of

a straight chain or branched C_{1-10} alkyl group,
a halogen atom selected from fluorine, chlorine, and bromine,
an acyl group,
an oxo group, and
an halo-C_{1-4} lower alkyl group having a halogen atom selected from fluorine, chlorine, and bromine; and

R_2 represents

a C_{1-4} lower alkyl groups that may have 1-3 substituents selected from the group consisting of

a C_{1-4} lower alkoxy group,
an amino group that may be substituted with a C_{1-4} lower alkyl or acyl group,
a C_{1-4} lower alkylthio group,
a carbamoyl group,
a hydroxyl group,
a carboxyl group,
an acyl group, and
a 5- or 6-membered heterocyclic group having 1-3 nitrogen, oxygen, or sulfur atoms; or

an aryl group that may have 1-4 substituents selected from the group consisting of

a C_{1-4} lower alkyl group,
a halogen atom selected from fluorine, chlorine, and bromine,
a nitro group,
a hydroxyl group,
a C_{1-4} lower alkoxy group,
a C_{1-4} lower alkylthio group,
an acyl group,
an amino group that may be substituted with a C_{1-4} lower alkyl or acyl group, and
a halo-C_{1-4} lower alkyl group having a halogen atom selected from fluorine, chlorine, and bromine,

a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

5. The CETP activity inhibitor comprising as an active ingredient the compound as claimed in claim 1, which is selected from the group consisting of

bis-[2-(pivaloylamino)phenyl] disulfide;
bis-[2-(2-propylpentanoylamino)phenyl] disulfide;
bis-[2-(1-methylcyclohexanecarbonylamino)phenyl] disulfide;
bis-[2-(1-isopentylcyclopentanecarbonylamino)phenyl] disulfide;

bis-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] disulfide;
N-(2-mercaptophenyl)-2,2-dimethylpropioneamide;
N-(2-mercaptophenyl)-1-isopentylcyclohexanecarboxamide;
N-(2-mercaptophenyl)-1-methylcyclohexanecarboxamide;
N-(2-mercaptophenyl)-1-isopentylcyclopentanecarboxamide;
N-(2-mercaptophenyl)-1-isopropylcyclohexanecarboxamide;
N-(4,5-dichloro-2-mercaptophenyl)-1-isopentylcyclohexanecarboxamide;
N-(4,5-dichloro-2-mercaptophenyl)-1-isopentylcyclopentanecarboxamide;
N-(2-mercapto-5-methylphenyl)-1-isopentylcyclohexanecarboxamide;
N-(2-mercapto-4-methylphenyl)-1-isopentylcyclohexanecarboxamide;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl]thioacetate;
S-[2-(1-methylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[2-(pivaloylamino)phenyl]phenylthioacetate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2-acetylamino-3-phenylthiopropionate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] 3-pyridinethiocarboxylate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] chlorothioacetate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] methoxythioacetate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] thiopropionate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] phenoxythioacetate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2-methylthiopropionate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] 4-chlorophenoxythioacetate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] cyclopropanethiocarboxylate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2-acetylamino-4-carbamoylthiobutyrate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2-hydroxy-2-methylthiopropionate;
S-[2-(1-isopentylcyclopentanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[2-(1-isopentylcyclopentanecarbonylamino)phenyl] thioacetate;
S-[4,5-dichloro-2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[4,5-dichloro-2-(1-isopentylcyclopentanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[2-(1-isopentylcyclohexanecarbonylamino)-4-trifluoromethylphenyl] 2,2-dimethylthiopropionate;
O-methyl S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl monothiocarbonate;
S-[2-(1-methylcyclohexanecarbonylamino)phenyl] S-phenyl dithiocarbonate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] N-phenylthiocarbamate;
S-[2-(pivaloylamino)-4-trifluoromethylphenyl] 2,2-dimethylthiopropionate;
S-(4,5-dichloro-2-(1-cyclopropylcyclohexanecarbonylamino) phenyl] 2,2-dimethylthiopropionate;
S-[4,5-dichloro-2-(2-cyclohexylpropionylamino)phenyl] 2,2-dimethylthiopropionate;
S-[4,5-dichloro-2-(1-pentylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[4,5-dichloro-2-(1-cyclopropylmethylcyclohexane carbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[4,5-dichloro-2-(1-cyclohexylmethylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[4,5-dichloro-2-(1-isopropylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[4,5-dichloro-2-(1-isopentylcycloheptanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[4,5-dichloro-2-(1-isopentylcyclobutanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[2-(1-isopentylcyclohexanecarbonylamino)-4-nitrophenyl] 2,2-dimethylthiopropionate;
S-[4-cyano-2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[4-chloro-2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropiornate;
S-[5-chloro-2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[4-fluoro-2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[(4,5-difluoro-2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[5-fluoro-2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
bis-[4,5-dichloro-2-(1-isopentylcyclohexanecarbonylamino)phenyl] disulfide;
2-tetrahydrofurylmethyl 2-(1-isopentylcyclohexanecarbonyl amino)phenyl disulfide;
N-(2-mercaptophenyl)-1-ethylcyclohexanecarboxamide;
N-(2-mercaptophenyl)-1-propylcyclohexanecarboxamide;
N-(2-mercaptophenyl)-1-butylcyclohexanecarboxamide;
N-(2-mercaptophenyl)-1-isobutylcyclohexanecarboxamide;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] cyclohexanethiocarboxylate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] thiobenzoate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] 5-carboxythiopentanoate;

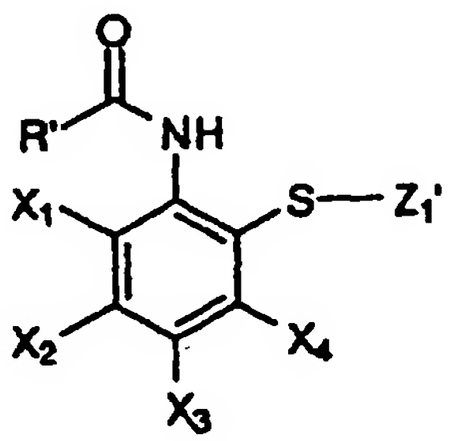
S-[2-(1-isopentylcyclohexanecarbonylamino)-4-methylphenyl] thioacetate;
bis-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl] disulfide;
N-(2-mercaptophenyl)-1-(2-ethylbutyl)cyclohexanecarboxamide;
S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl] 2-methylthiopropionate;
S-[2-(1-isobutylcyclohexanecarbonylamino)phenyl] 2-methylthiopropionate;
S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl] 1-acetylpiperidine-4-thiocarboxylate;
S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl] thioacetate;
S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl] 2,2-dimethylthiopropionate;
S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl] methoxythioacetate;
S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl] 2-hydroxy-2-methylthiopropionate;
S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl] 4-chlorophenoxythioacetate;
S-[2-(1-isobutylcyclohexanecarbonylamino)phenyl] 4-chlorophenoxythioacetate; and
S-[2-(1-isobutylcyclohexanecarbonylamino)phenyl] 1-acetylpiperidine-4-thiocarboxylate,

a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

6. A prophylactic or therapeutic agent for hyperlipidemia comprising as an active ingredient the compound as claimed in any of claims 1-5, a prodrug compound, a pharmaceutically acceptable salt, or hydrate or solvate thereof.

7. A prophylactic or therapeutic agent for atherosclerosis comprising as an active ingredient the compound as claimed in any of claims 1-5, a prodrug compound, a pharmaceutically acceptable salt, or hydrate or solvate thereof.

8. A Compound represented by the formula (I-2):



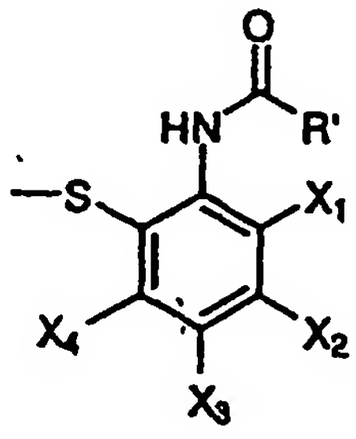
(I-2)

wherein R' represents

a substituted or unsubstituted C_{3-10} cycloalkyl group or
a substituted or unsubstituted C_{5-8} cycloalkenyl group;

X_1, X_2, X_3, and X_4 are defined as in claim 1; and Z_1' represents

a hydrogen atom;
a group represented by the formula:



wherein R', X_1, X_2, X_3, and X_4 are as described above;

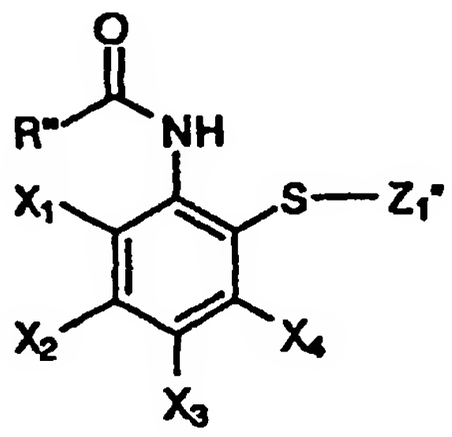
$-Y_1R_1$,

wherein Y_1 and R_1 are the same as in claim 3; or

$-S-R_2$,

wherein R_2 is the same as in claim 3,
a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

9. A compound as claimed in claim 8, which is represented by the formula (I-3):



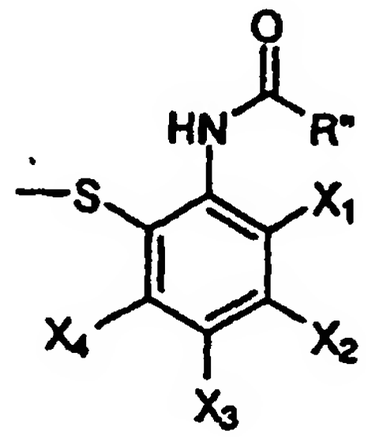
(I-3)

wherein R" represents

a 1-substituted-C_{3-10} cycloalkyl group or
a 1-substituted-C_{5-8} cycloalkenyl group;

X_1, X_2, X_3, and X_4 are the same as in claim 1; and Z_1" represents

a hydrogen atoms;
a group represented by the formula:



wherein R", X_1, X_2, X_3, and X_4 are as described above;

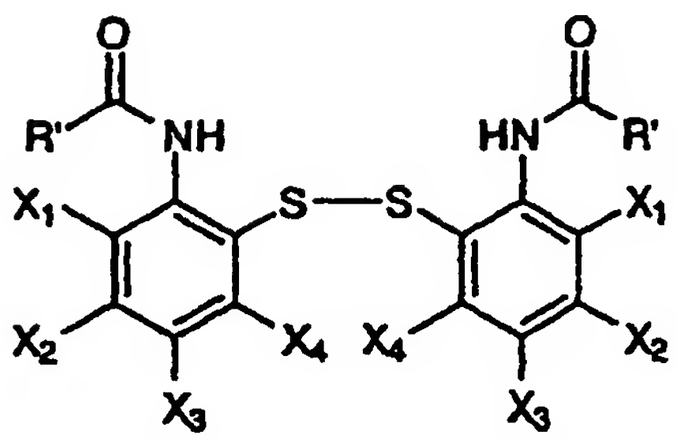
$-Y_1R_1$,

wherein Y_1 and R_1 are the same as in claim 3; or

$-S-R_2$,

wherein R_2 is the same as in claim 3,
a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

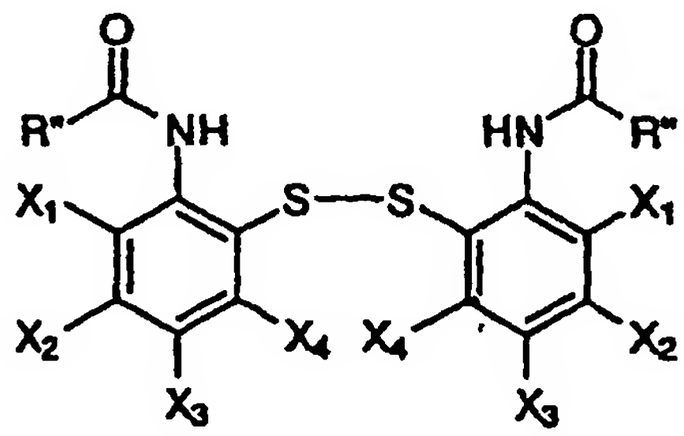
10. A compound as claimed in claim 8, which is represented by the formula (II):



(II)

wherein R', X_1, X_2, X_3, and X_4 are the same as in claim 8,
a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

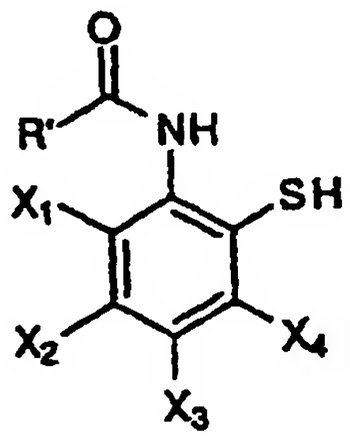
11. A compound as claimed in claim 9, which is represented by formula (II-1):



(II-1)

wherein R", X_1, X_2, X_3, and X_4 are the same as in claim 9,
a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

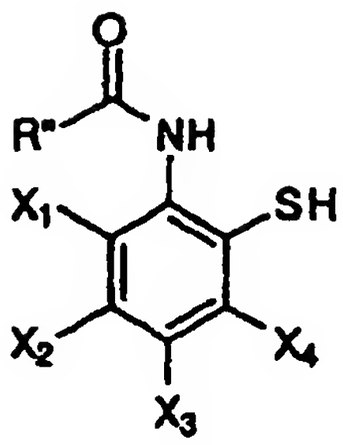
12. A compound as claimed in claim 8, which represented by the formula (III):



(III)

wherein R', X_1, X_2, X_3, and X_4 are the same as in claim 8,
a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

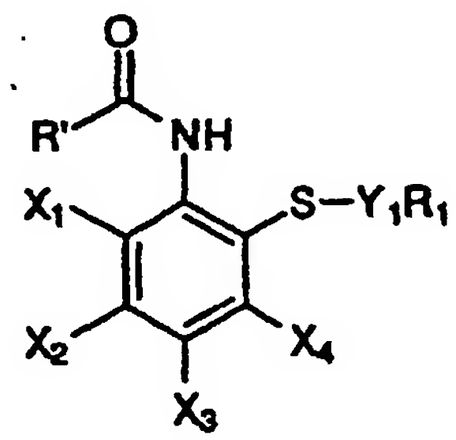
13. A compound as claimed in claim 9, which is represented by formula (III-1):



(III-1)

wherein R", X_1, X_2, X_3, and X_4 are the same as in claim 9,
a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

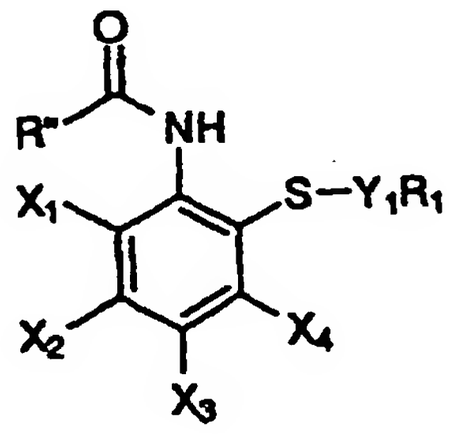
14. A compound as claimed in claim 8, which is represented by formula (IV):



(IV)

wherein R', X_1, X_2, X_3, X_4, Y_1, and R_1 are the same as in claim 8, a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

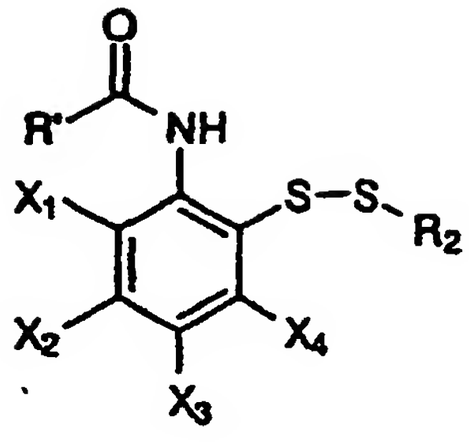
15. A compound as claimed in claim 9, which is represented by formula (IV-1):



(IV-1)

wherein R", X_1, X_2, X_3, X_4, Y_1, and R_1 are the same as in claim 9, a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

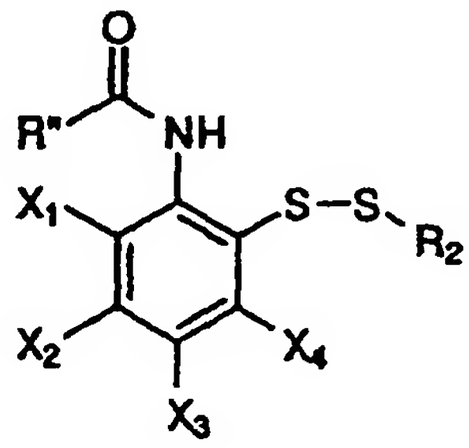
16. A compound as claimed in claim 8, which is represented by formula (V):



(V)

wherein R', X_1, X_2, X_3, X_4, and R_2 are the same as in claim 8, a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

17. A compound as claimed in claim 9, which is represented by formula (V-1):



(V-1)

wherein R", X_1, X_2, X_3, X_4, and R_2 are the same as in claim 9, a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

18. A compound as claimed in claim 8, which is selected from the group consisting of

bis-[2-(1-methylcyclohexanecarbonylamino)phenyl] disulfide;
bis-[2-(1-isopentylcyclopentanecarbonylamino)phenyl] disulfide;
bis-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] disulfide;
N-(2-mercaptophenyl)-1-isopentylcyclohexanecarboxamide;
N-(2-mercaptophenyl)-1-methylcyclohexanecarboxamide;
N-(2-mercaptophenyl)-1-isopentylcyclopentanecarboxamide;
N-(2-mercaptophenyl)-1-isopropylcyclohexanecarboxamide;
N-(4,5-dichloro-2-mercaptophenyl)-1-isopentylcyclohexanecarboxamide;
N-(4,5-dichloro-2-mercaptophenyl)-1-isopentylcyclopentanecarboxamide;
N-(2-mercapto-5-methylphenyl)-1-isopentylcyclohexanecarboxamide;
N-(2-mercapto-4-methylphenyl)-1-isopentylcyclohexanecarboxamide;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] thioacetate;
S-[2-(1-methylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2-acetylamino-3-phenylthiopropionate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] 3-pyridinethiocarboxylate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] chlorothioacetate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] methoxythioacetate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] thiopropionate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] phenoxythioacetate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2-methylthiopropionate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] 4-chlorophenoxythioacetate;

S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] cyclopropanethiocarboxylate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2-acetylamino-4-carbamoylthiobutyrate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2-hydroxy-2-methylthiopropionate;
S-[2-(1-isopentylcyclopentanecarbonylamino)phenyl] 2,2-dimethylpropionate;
S-[2-(1-isopentylcyclopentanecarbonylamino)phenyl] thioacetate;
S-[4,5-dichloro-2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[4,5-dichloro-2-(1-isopentylcyclopentanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[2-(1-isopentylcyclohexanecarbonylamino) -4-trifluoromethylphenyl] 2,2-dimethylthiopropionate;
O-methyl S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] monothiocarbonate;
S-[2-(1-methylcyclohexanecarbonylamino)phenyl] S-phenyl dithiocarbonate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] N-phenylthiocarbamate;
S-[4,5-dichloro-2-(1-cyclopropylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[4,5-dichloro-2-(1-pentylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[4,5-dichloro-2-(1-cyclopropylmethylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[4,5-dichloro-2-(1-cyclohexylmethylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropioate;
S-[4,5-dichloro-2-(1-isopropylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[4,5-dichloro-2-(1-isopentylcycloheptanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[4,5-dichloro-2-(1-isopentylcyclobutanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[2-(1-isopentylcyclohexanecarbonylamino)-4-nitrophenyl] 2,2-dimethylthiopropionate;
S-[4-cyano-2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[4-chloro-2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[5-chloro-2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[4-fluoro-2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[4,5-difluoro-2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
S-[5-fluoro-2-(1-isopentylcyclohexanecarbonylamino)phenyl] 2,2-dimethylthiopropionate;
bis-[4,5-dichloro-2-(1-isopentylcyclohexanecarbonylamino)phenyl] disulfide;
2-tetrahydrofurylmethyl 2-(1-isopentylcyclohexanecarbonylamino)phenyl disulfide;
N-(2-mercaptophenyl)-1-ethylcyclohexanecarboxamide;
N-(2-mercaptophenyl)-1-propylcyclohexanecarboxamide;
N-(2-mercaptophenyl)-1-butylcyclohexanecarboxamide;
N-(2-mercaptophenyl)-1-isobutylcyclohexanecarboxamide;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] cyclohexanethiocarboxylate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] thiobenzoate;
S-[2-(1-isopentylcyclohexanecarbonylamino)phenyl] 5-carboxythiopentanoate;
S-[2-(1-isopentylcyclohexanecarbonylamino)-4-methylphenyl] thioacetate;
bis-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl] disulfide;
N-(2-mercaptophenyl)-1-(2-ethylbutyl)cyclohexanecarboxamide;
S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl] 2-methylthiopropionate;
S-[2-(1-isobutylcyclohexanecarbonylamino]phenyl] 2-methylthiopropionate;
S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl] 1-acetylpiperidine-4-thiocarboxylate;
S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl] thioacetate;
S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl] 2,2-dimethylthiopropionate;
S-[2-(1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl] methoxythioacetate;
S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl] 2-hydroxy-2-methylpropionate;
S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]phenyl] 4-chlorophenoxythioacetate;
S-[2-(1-isobutylcyclohexanecarbonylamino)phenyl] 4-chlorophenoxythioacetate; and
S-[2-(1-isobutylcyclohexanecarbonylamino)phenyl] 1-acetylpiperidine-4-thiocarboxylate,

a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

19. A pharmaceutical composition comprising as an active ingredient the compound as claimed in any of claims 8-18, a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

20. Use of the compound represented by the formula (I), a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof, for production of a CETP activity inhibitor.

21. Use of the compound represented by the formula (I), a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof, for production of a prophylactic or therapeutic agent for hyperlipidemia.

22. Use of the compound represented by the formula (I), a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof, for production of a prophylactic or therapeutic agent for atherosclerosis.

23. A method for inhibition of CETP activity comprising administering to patients the compound represented by the formula (I), a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

24. A method for prevention or therapy of hyperlipidemia comprising administering to patients the compound represented by the formula (I), a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

25. A method for prevention or therapy of atherosclerosis comprising administering to patients the compound represented by the formula (I), a prodrug compound, a pharmaceutically acceptable salt, hydrate, or solvate thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP98/00542

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl⁶ C07C323/40, C07C323/63, C07C323/65, C07D207/16, C07D207/28, C07D211/62, C07D213/81, C07D307/68, C07D333/38, A61K31/165,
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl⁶ C07C323/40, C07C323/63, C07C323/65, C07D207/16, C07D207/28, C07D211/62, C07D213/81, C07D307/68, C07D333/38, A61K31/165,

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS (STN), WPI (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X/ A	WO, 95/01326, A1 (Wellcome Foundation Ltd.), January 12, 1995 (12. 01. 95) & EP, 706508, A1 & JP, 8-512046, A	7, 22 / 1-6, 8-21
A	EP, 632036, A1 (Sankyo Co., Ltd.), January 2, 1995 (02. 01. 95) & US, 5534529, A & JP, 7-70021, A	1-22
A	WO, 92/03412, A1 (Rhone-oulenc Rorer Ltd.), March 5, 1992 (05. 03. 92) & EP, 543865, A1 & JP, 6-500315, A	1-22
A	WO, 92/03408, A1 (Rhone-oulenc Rorer Ltd.), March 5, 1992 (05. 03. 92) & EP, 543884, A1 & JP, 6-500083, A	1-22
P, A	EP, 796846, A1 (Bayer A.-G.), September 24, 1997 (24. 09. 97) & JP, 9-255574, A	1-22

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
April 10, 1998 (10. 04. 98)	April 21, 1998 (21. 04. 98)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP98/00542

A. (Continuation) CLASSIFICATION OF SUBJECT MATTER

A61K31/18, A61K31/255, A61K31/34, A61K31/38, A61K31/40, A61K31/44

B. (Continuation) FIELDS SEARCHED

A61K31/18, A61K31/255, A61K31/34, A61K31/38, A61K31/40, A61K31/44

Form PCT/ISA/210 (extra sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP98/00542

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 23-25

because they relate to subject matter not required to be searched by this Authority, namely:

Claims 23 to 25 pertain to methods for treatment of the human body by therapy and thus relate to a subject matter which this International Searching Authority is not required, under the provisions of Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the

2. [ ] Claims Nos.:

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP98/00542

Continuation of Box No. I of continuation of first sheet (1)

PCT, to search.

Form PCT/ISA/210 (extra sheet) (July 1992)

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International Bureau

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PCT

(10) International Publication Number
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(30) Priority Data:
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(72) Inventors; and

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(74) Agents: **SPIEGEL, Allen, J.** et al.; c/o Simpson, Alison, Urquhart-Dykes & Lord, 30 Welbeck Street, London W1G 8ER (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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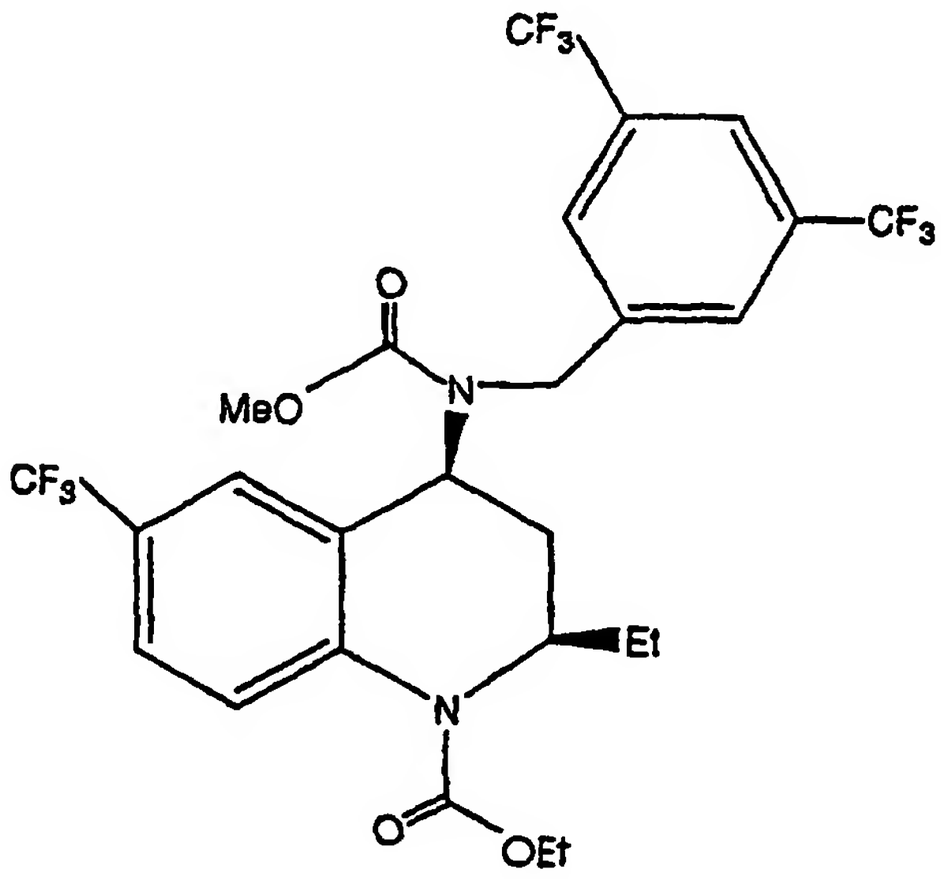
Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 4-CARBOXYAMINO-2-ETHYL-1,2,3,4-TETRAHYDROQUINOLINE CRYSTAL AS CETP INHIBITOR

(57) Abstract: Crystalline forms of a CETP inhibitor of formula (I), methods of making the crystals, methods of using the crystals and pharmaceutically compositions containing the crystals are disclosed.



(I)

WO 01/40190 A1

4-CARBOXYAMINO-2-ETHYL-1,2,3,4-TETRAHYDROQUINOLINE CRYSTAL AS CETP INHIBITOR

Background Of The Invention

This invention relates to cholesteryl ester transfer protein (CETP) inhibitors, pharmaceutical compositions containing such inhibitors and the use of such inhibitors to elevate certain plasma lipid levels, including high density lipoprotein (HDL)-cholesterol and to lower certain other plasma lipid levels, such as low density lipoprotein (LDL)-cholesterol and triglycerides and accordingly to treat diseases which are affected by low levels of HDL cholesterol and/or high levels of LDL-cholesterol and triglycerides, such as atherosclerosis and cardiovascular diseases in certain mammals (i.e., those which have CETP in their plasma), including humans.

More particularly, this invention relates to CETP inhibitor crystals, pharmaceutical compositions comprising these crystals, a process for preparing these crystals and to methods of treating atherosclerosis, obesity, and related diseases and/or conditions with the crystals.

Atherosclerosis and its associated coronary artery disease (CAD) is the leading cause of mortality in the industrialized world. Despite attempts to modify secondary risk factors (smoking, obesity, lack of exercise) and treatment of dyslipidemia with dietary modification and drug therapy, coronary heart disease (CHD) remains the most common cause of death in the U.S., where cardiovascular disease accounts for 44% of all deaths, with 53% of these associated with atherosclerotic coronary heart disease.

Risk for development of this condition has been shown to be strongly correlated with certain plasma lipid levels. While elevated LDL-cholesterol may be the most recognized form of dyslipidemia, it is by no means the only significant lipid associated contributor to CHD. Low HDL-cholesterol is also a known risk factor for CHD (Gordon, D.J., et al.,: "High-density Lipoprotein Cholesterol and Cardiovascular Disease", Circulation, (1989), 79: 8-15).

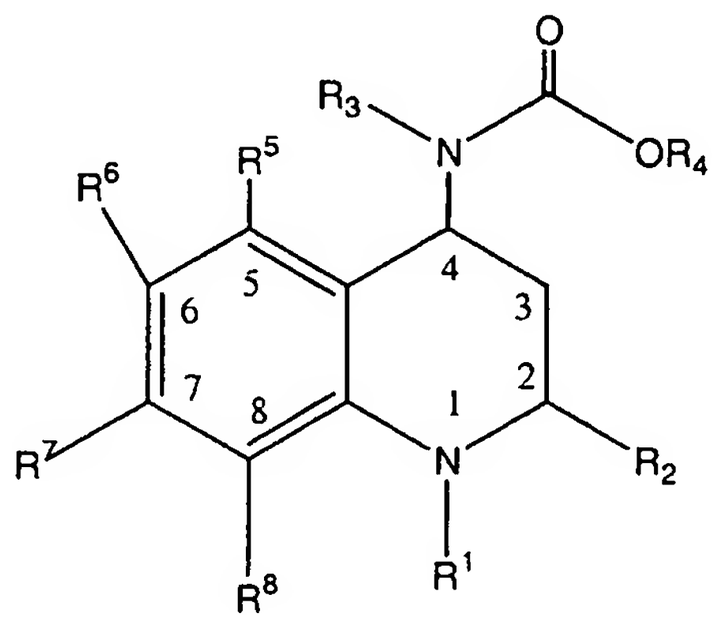
High LDL-cholesterol and triglyceride levels are positively correlated, while high levels of HDL-cholesterol are negatively correlated with the risk for developing cardiovascular diseases. Thus, dyslipidemia is not a unitary risk profile for CHD but may be comprised of one or more lipid aberrations.

Among the many factors controlling plasma levels of these disease dependent principles, cholesteryl ester transfer protein (CETP) activity affects all

three. The role of this 70,000 dalton plasma glycoprotein found in a number of animal species, including humans, is to transfer cholesteryl ester and triglyceride between lipoprotein particles, including high density lipoproteins (HDL), low density lipoproteins (LDL), very low density lipoproteins (VLDL), and chylomicrons. The net result of CETP activity is a lowering of HDL cholesterol and an increase in LDL cholesterol. This effect on lipoprotein profile is believed to be pro-atherogenic, especially in subjects whose lipid profile constitutes an increased risk for CHD.

No wholly satisfactory HDL-elevating therapies exist. Niacin can significantly increase HDL, but has serious toleration issues which reduce compliance. Fibrates and the HMG CoA reductase inhibitors raise HDL-C only modestly (~10-12%). As a result, there is a significant unmet medical need for a well-tolerated agent which can significantly elevate plasma HDL levels, thereby reversing or slowing the progression of atherosclerosis.

Commonly assigned U.S. application ser. No. 09/391,152 filed September 7, 1999 entitled 4-CARBOXYAMINO-2-SUBSTITUTED-1,2,3,4-TETRAHYDROQUINOLINES, the disclosure of which is hereby incorporated by reference, is directed to compounds of the following general formula:

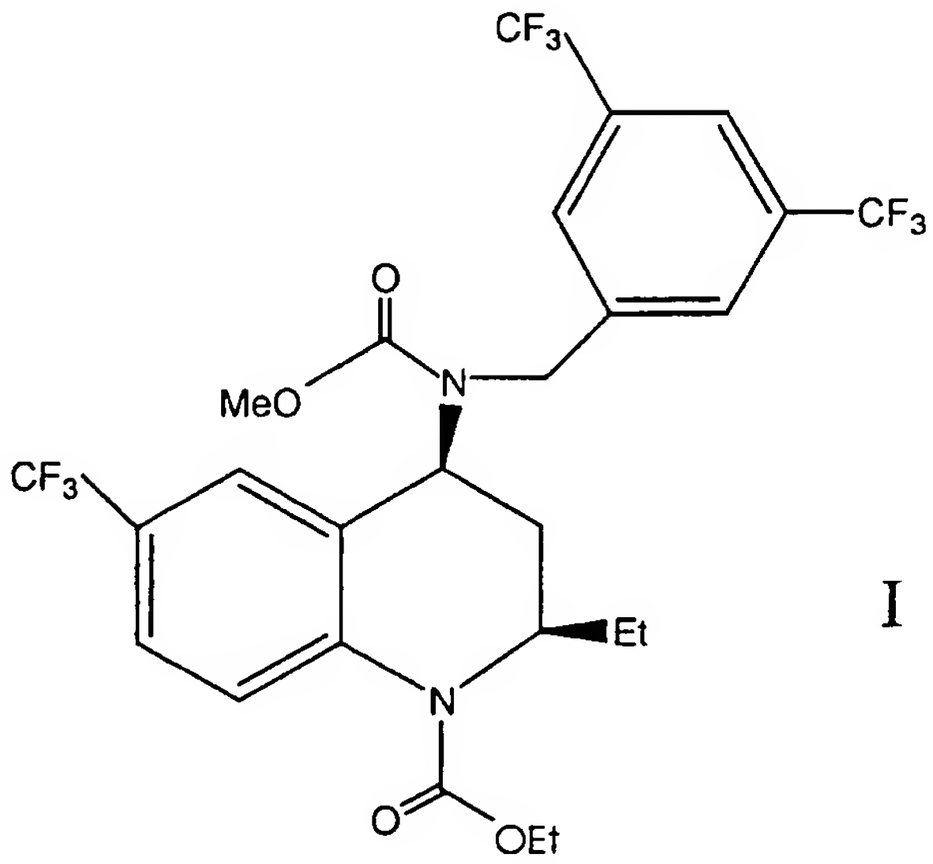


Specifically, the compound [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester is described.

Thus, although there are a variety of anti-atherosclerosis therapies, there is a continuing need and a continuing search in this field of art for alternative therapies.

Summary Of The Invention

This invention is directed to a Formula I crystal



I

Alternatively, a crystal of the above Formula I is named as [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester.

Another aspect of this invention is directed to an anhydrous crystal of Formula I.

Another aspect of this invention is directed to the corresponding anhydrous crystal having the X-ray powder diffraction pattern as shown in Figure 1.

Another aspect of this invention is directed to an ethanolate crystal of Formula I.

Another aspect of this invention is directed to the corresponding ethanolate crystal having the X-ray powder diffraction pattern as shown in Figure 2.

A preferred dosage is about 0.01 to 100 mg/kg/day of a Formula I crystal. An especially preferred dosage is about 0.1 to 10 mg/kg/day of a Formula I crystal.

In the text herein including the following methods, pharmaceutical compositions, combinations and kits reference is made to a crystal of Formula I. While it is understood that if the crystal is in solution, the crystal form is not present (in contrast to e.g., a dry tablet formulation), the following methods pharmaceutical compositions combinations and kits are intended to include a method or formulation

resulting from a use of such crystal (e.g., administering a gelatin capsule including an oil formulation solution of the crystal).

Yet another aspect of this invention is directed to methods for treating atherosclerosis, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia, cardiovascular disorders, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, vascular complications of diabetes, obesity or endotoxemia in a mammal (including a human being either male or female) by administering to a mammal in need of such treatment an atherosclerosis, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia, cardiovascular disorders, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, vascular complications of diabetes, obesity or endotoxemia treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating atherosclerosis in a mammal (including a human being) by administering to a mammal in need of such treatment an atherosclerosis treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating peripheral vascular disease in a mammal (including a human being) by administering to a mammal in need of such treatment a peripheral vascular disease treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating dyslipidemia in a mammal (including a human being) by administering to a mammal in need of such treatment a dyslipidemia treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating hyperbetalipoproteinemia in a mammal (including a human being) by administering to a mammal in need of such treatment a hyperbetalipoproteinemia treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating hypoalphalipoproteinemia in a mammal (including a human being) by administering to a mammal in need of such treatment a hypoalphalipoproteinemia treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating hypercholesterolemia in a mammal (including a human being) by administering to a mammal in need of such treatment a hypercholesterolemia treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating hypertriglyceridemia in a mammal (including a human being) by administering to a mammal in need of such treatment a hypertriglyceridemia treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating familial-hypercholesterolemia in a mammal (including a human being) by administering to a mammal in need of such treatment a familial-hypercholesterolemia treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating cardiovascular disorders in a mammal (including a human being) by administering to a mammal in need of such treatment a cardiovascular disorder treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating angina in a mammal (including a human being) by administering to a mammal in need of such treatment an angina treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating ischemia in a mammal (including a human being) by administering to a mammal in need of such treatment an ischemic disease treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating cardiac ischemia in a mammal (including a human being) by administering to a mammal in need of such treatment a cardiac ischemic treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating stroke in a mammal (including a human being) by administering to a mammal in need of such treatment a stroke treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating a myocardial infarction in a mammal (including a human being) by administering to a mammal in need of such treatment a myocardial infarction treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating reperfusion injury in a mammal (including a human being) by administering to a mammal in need of such treatment a reperfusion injury treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating angioplastic restenosis in a mammal (including a human being) by administering to a mammal in need of such treatment an angioplastic restenosis treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating hypertension in a mammal (including a human being) by administering to a mammal in need of such treatment a hypertension treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating the vascular complications of diabetes in a mammal (including a human being) by administering to a mammal in need of such treatment a vascular complications of diabetes treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating obesity in a mammal (including a human being) by administering to a mammal in need of such treatment an obesity treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating endotoxemia in a mammal (including a human being) by administering to a mammal in need of such treatment an endotoxemia treating amount of a Formula I crystal.

This invention is also directed to pharmaceutical compositions which comprise a therapeutically effective amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of atherosclerosis, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia, cardiovascular disorders, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, vascular complications of diabetes, obesity or endotoxemia in a mammal (including a human being) which comprise a therapeutically effective amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of atherosclerosis in a mammal (including a human being) which comprise an atherosclerosis treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of peripheral vascular disease in a mammal (including a human being) which comprise a peripheral vascular disease treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of dyslipidemia in a mammal (including a human being) which comprise a dyslipidemia treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of hyperbetalipoproteinemia in a mammal (including a human being) which comprise a hyperbetalipoproteinemia treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of hypoalphalipoproteinemia in a mammal (including a human being) which comprise a hypoalphalipoproteinemia treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of hypercholesterolemia in a mammal (including a human being) which comprise a hypercholesterolemia treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of hypertriglyceridemia in a mammal (including a human being) which comprise a hypertriglyceridemia treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of familial-hypercholesterolemia in a mammal (including a human being) which comprise a familial-hypercholesterolemia treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of angina in a mammal (including a human being) which comprise an

angina treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of ischemia in a mammal (including a human being) which comprise an ischemic treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of cardiac ischemia in a mammal (including a human being) which comprise a cardiac ischemic treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of stroke in a mammal (including a human being) which comprise a stroke treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of a myocardial infarction in a mammal (including a human being) which comprise a myocardial infarction treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of reperfusion injury in a mammal (including a human being) which comprise a reperfusion injury treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent..

This invention is also directed to pharmaceutical compositions for the treatment of angioplastic restenosis in a mammal (including a human being) which comprise an angioplastic restenosis treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of hypertension in a mammal (including a human being) which comprise a hypertension treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of the vascular complications of diabetes in a mammal (including a human being) which comprise a vascular complications of diabetes treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of obesity in a mammal (including a human being) which comprise an obesity treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of endotoxemia in a mammal (including a human being) which comprise an endotoxemia treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to a pharmaceutical combination composition comprising: a therapeutically effective amount of a composition comprising

a first compound, said first compound being a Formula I crystal;

a second compound, said second compound being an HMG-CoA reductase inhibitor, an microsomal triglyceride transfer protein (MTP)/Apo B secretion inhibitor, a PPAR activator, a bile acid reuptake inhibitor, a cholesterol absorption inhibitor, a cholesterol synthesis inhibitor, a fibrate, niacin, an ion-exchange resin, an antioxidant, an ACAT inhibitor or a bile acid sequestrant; and/or optionally

a pharmaceutical carrier, vehicle or diluent.

Preferred among the second compounds are an HMG-CoA reductase inhibitor and a MTP/Apo B secretion inhibitor.

A particularly preferred HMG-CoA reductase inhibitor is lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin or rivastatin.

Another aspect of this invention is a method for treating atherosclerosis in a mammal comprising administering to a mammal suffering from atherosclerosis

a first compound, said first compound being a Formula I crystal; and

a second compound, said second compound being an HMG-CoA reductase inhibitor, an MTP/Apo B secretion inhibitor, a cholesterol absorption inhibitor, a cholesterol synthesis inhibitor, a fibrate, niacin, an ion-exchange resin, an antioxidant, an ACAT inhibitor or a bile acid sequestrant wherein the amounts of the first and second compounds result in a therapeutic effect.

A preferred aspect of the above method is wherein the second compound is an HMG-CoA reductase inhibitor or an MTP/Apo B secretion inhibitor.

A particularly preferred aspect of the above method is wherein the HMG-CoA reductase inhibitor is lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin or rivastatin.

Yet another aspect of this invention is a kit comprising:

a. a first compound, said first compound being a Formula I crystal, and a pharmaceutically acceptable carrier in a first in a unit dosage form;

b. a second compound, said second compound being an HMG CoA reductase inhibitor, an MTP/Apo B secretion inhibitor, a cholesterol absorption inhibitor, a cholesterol synthesis inhibitor, a fibrate, niacin, an ion-exchange resin, an antioxidant, an ACAT inhibitor or a bile acid sequestrant and a pharmaceutically acceptable carrier in a second unit dosage form; and

c. means for containing said first and second dosage forms wherein the amounts of the first and second compounds result in a therapeutic effect.

A preferred second compound is an HMG-CoA reductase inhibitor or an MTP/Apo B secretion inhibitor.

A particularly preferred HMG-CoA reductase inhibitor is lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin or rivastatin.

The present invention is also directed to processes for preparing crystalline anhydrous [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester by dissolving or mixing [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester in the presence of a suitable organic solvent, preferably hexanes.

Another aspect of this invention is directed to a process for preparing crystalline ethanolate [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester by dissolving or mixing [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester in ethanol/water at ambient temperature for about 0.5 to about 18 hours. Preferably ethanol is used without water.

This invention is also directed to a process for preparing crystalline anhydrous [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester comprising dissolving or mixing [2R,4S] 4-[3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester in ethanol at ambient temperature for about 2 to about 24 hours.

It is noted that as the anhydrous and ethanolate crystals are of different energy levels seeding with either anhydrous or ethanolate may determine the resulting isolated crystalline form. As is known in the art the presence of seed crystals in the air in a lab may be sufficient "seeding." In one embodiment anhydrous crystals may be obtained using hexanes and the resulting anhydrous crystals may be used to seed the production of further anhydrous crystals from ethanol.

As used herein the term mammals is meant to refer to all mammals which contain CETP in their plasma, for example, rabbits and primates such as monkeys and humans. Certain other mammals e.g., dogs, cats, cattle, goats, sheep and horses do not contain CETP in their plasma and so are not included herein.

The term ethanolate refers to an ethanol of solvation.

The term "treating", "treat" or "treatment" as used herein includes preventative (e.g., prophylactic) and palliative treatment.

By "pharmaceutically acceptable" it is meant the carrier, vehicle, diluent, excipients, and/or salt must be compatible with the other ingredients of the formulation, and not deleterious to the recipient thereof.

As used herein, the expressions "reaction-inert solvent" and "inert solvent" refers to a solvent or mixture of solvents which does not interact with starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

It will be recognized that the compound of this invention can exist in radiolabelled form, i.e., said compound may contain one or more atoms containing an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Radioisotopes of hydrogen, carbon, phosphorous, fluorine and chlorine include ^{3}H, ^{14}C, ^{32}P, ^{35}S, ^{18}F and ^{36}Cl, respectively. The compound of this invention which contains those radioisotopes and/or other radioisotopes of other atoms is within the scope of this invention. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, radioisotopes are particularly preferred for their ease of preparation and detectability. A radiolabelled compound of this invention can generally be prepared by methods well known to those skilled in the art. Conveniently, such radiolabelled compounds can be prepared by carrying out the procedures disclosed in the Examples below by substituting a readily available radiolabelled reagent for a non-radiolabelled reagent.

Other features and advantages will be apparent from the specification and claims which describe the invention.

Brief Description of the Drawings

FIG. 1 is a characteristic x-ray powder diffraction pattern showing that anhydrous [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester is crystalline. (Vertical Axis: Intensity (CPS); Horizontal Axis: Two theta (degrees))

FIG. 2 is the characteristic x-ray powder diffraction pattern of the ethanolate [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester as crystalline Vertical Axis: Intensity (CPS); Horizontal Axis: Two theta (degrees))

Detailed Description Of The Invention

In general the compound of this invention can be made by processes which include analogous processes known in the chemical arts, particularly in light of the description contained herein. Certain processes for the manufacture of the compound of this invention are provided as further features of the invention and are described below including in the Examples.

The amorphous form of the compound of this invention [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester is prepared as disclosed below (see Example 1).

An anhydrous crystalline form of the above compound may be prepared from the amorphous compound by recrystallization from hexanes (solvent comprised of hexane isomers (e.g., n-hexane, cyclohexane, methyl pentane, etc.)) at a temperature of about 40°C to about 80°C, preferably 60° followed typically by granulating, for about 2 to about 24 hours, then filtering the material and subsequent air drying.

Alternatively, the anhydrous crystal may be prepared from the ethanolate crystalline form (described below) utilizing analogous procedures to the immediately preceding procedure. In addition, the yield in this procedure may be enhanced by azeotroping the ethanol from the hexanes.

An ethanolate crystalline form of the above compound may be prepared from the amorphous compound by recrystallization from ethanol/water at a temperature of about 20°C to about 25°C, preferably ambient temperature for about 0.5 hour to about 18 hours. Typically the range is about 3% to about 10% ethanol and about

90% to about 97% water. Preferably the ratio is about 10% to about 90% ethanol/water.

Alternatively, the ethanolate crystalline form may be prepared utilizing procedures analogous to those described above but using ethanol alone. The filtered materials are typically granulated for about 2 hours to about 24 hours followed by air drying.

The following Table 1 details important properties for three forms of [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester: the amorphous (A); and the two crystalline forms ethanolate (B) and crystalline anhydrous (C).

TABLE 1

	Thermal Stability	Crystallinity	Solubility	Stability
Amorphous A	M.P. 21°C	Non-crystalline	Most soluble in aqueous	hygrocopic
[1]Ethanolate B (Fig. 2)	Melt onset 45°C	Crystalline	Higher solubility in aqueous than Anhydrous (C)	non-hygroscopic @ 90% relative humidity over 24 hours
Anhydrous C (Fig. 1)	M.P. 89-90°C	Crystalline	Least soluble in water	non-hygroscopic at 80% & 100% relative humidity over 3 days.

[1]Loses some ethanol at closed bottle ambient conditions but remains crystalline

The compound of the instant invention is orally administrable and is accordingly used in combination with a pharmaceutically acceptable vehicle, carrier or diluent suitable to oral dosage forms. Suitable pharmaceutically-acceptable carriers include inert solid fillers or diluents and sterile aqueous or organic solutions. The active compound will be present in such pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described below. Thus, for oral administration the compound may be combined with a suitable solid or liquid carrier or diluent to form capsules, tablets, powders, syrups, solutions, suspensions and the like. The pharmaceutical compositions may, if desired, contain additional components such as flavorants, sweeteners, excipients and the like.

The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, for example a gel capsule, it may contain, in addition to or instead of materials of the above type, a liquid carrier such as a fatty glyceride or mixtures of fatty glycerides, such as olive oil, or Miglyol™ or Capmul™ glycerides. Dosage forms may also include orral suspensions.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a

sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

The compound of the instant invention may also be administered parenterally. For parenteral administration the compound may be combined with sterile aqueous or organic media to form injectable solutions or suspensions. The injectable solutions prepared in this manner can then be administered intravenously, intraperitoneally, subcutaneously, or intramuscularly.

The pharmaceutical forms suitable for injectable use include sterile solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. They may be sterilized, for example, by filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, or by irradiating or heating the compositions where such irradiating or heating is both appropriate and compatible with the drug formulation.

Additional pharmaceutical formulations may include, inter alia, suppositories, sublingual tablets, topical dosage forms and the like and these may be prepared according to methods which are commonly accepted in the art.

Controlled release, sustained release, and delayed release oral or parenteral compositions may be used.

The dosage of the compound of the instant invention which is administered will generally be varied according to principles well known in the art taking into account the severity of the condition being treated and the route of administration. In general, the compound will be administered to a warm blooded animal (such as a human, livestock or pet) so that an effective dose, usually a daily dose administered in unitary or divided portions, is received, for example a dose in the range of about 0.01 to about 100 mg/kg/day body weight, preferably about 0.1 to about 10 mg/kg/day body weight. The above dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such deviations are within the scope of this invention.

EXAMPLES

Melting points were determined with a Thomas Hoover melting point apparatus or a DSC apparatus. Unless otherwise stated, CD_3Cl_3 was used for NMR

spectra. Microanalysis was performed by Schwarzkopf Microanalytical Laboratory. All reagents and solvents were obtained commercially and used without purification.

Example 1

cis-4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester:

A solution of *cis*-4-(3,5-bis-trifluoromethyl-benzylamino)-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (2.0 g, 3.7 mmol) and pyridine (0.58 g, 7.4 mmol) in 100 mL of dichloromethane was cooled in an ice/water bath as methyl chloroformate (0.87 g, 9.2 mmol) was added slowly. After stirring overnight at room temperature, the reaction mixture was washed twice with a 2N hydrochloric acid solution, dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford the crude product, which was purified by silica gel chromatography using 5-10% ethyl acetate/hexanes as eluent to afford 1.8 g of the title product. MS *m/z* 601 ($M^+ + 1$); ^1H NMR (coalescing mixture of conformers, $CDCl_3$) δ 0.6-0.8 (bm, 3H), 1.2-1.3 (bm, 3H), 1.3-1.5 (bm, 2H), 1.6-1.75 (bm, 1H), 2.1-2.3 (bm, 1H), 3.7-3.9 (bs, 3H), 4.0-4.4 (bm, 4H), 5.0-5.6 (bm, 2H), 7.1 (s, 1H), 7.4-7.6 (bm, 2H), 7.6-7.8 (bm, 3H).

[2R,4S]4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester was prepared in optically enriched form by resolution of the corresponding racemate, or an intermediate in its synthesis, using standard methods.

Example 2

(1-Benzotriazol-1-yl-propyl)-(4-trifluoromethyl-phenyl)-amine

A two liter, four neck flask under nitrogen atmosphere was charged with benzotriazole (36.96 g, 310 mmol, 1.0 equiv) and dry toluene (400 mL). A room temperature solution of 4-(trifluoromethyl)aniline (39.1 mL, 310 mmol, 1.0 equiv) and 50 mL toluene was added over one minute. A room temperature solution of propionaldehyde (24.6 mL, 341 mmol, 1.1 equiv) and 50 mL toluene was then added over 20 minutes. There was an exotherm from 23°C to 30°C during this addition. After stirring 24 h, n-heptane (500 mL) was added, and the slurry stirred an additional 1 h. The suspension was filtered, the solids were washed with n-heptane (1 x 100 mL, then 1 x 200 mL, and dried. (1-Benzotriazol-1-yl-propyl)-(4-trifluoromethyl-phenyl)-amine was isolated as shiny white needles (81.3 g, 82%). After 24 h, a second crop was isolated from the filtrate (8.7 g, 9%). mp 130-132 °C; ^1H NMR

(DMSO-d6, 400 MHz) δ 0.82 (t, 3H, J=7.5 Hz), 2.25 (m, 2H), 6.49 (m, 1H), 6.80 (d, 2H, J=8.7 Hz), 7.35 (m, 3H), 7.50 (m, 1H), 7.88 (d, 1H, J=8.3 Hz), 7.99 (m, 1H), 8.09 (d, 1H, J=8.5 Hz); ^{13}C NMR (DMSO-d6, 100 MHz) δ 149.32, 146.19, 131.46, 127.73, 126.8, 125.33 (q, J=270 Hz), 124.44, 119.88, 118.27 (q, J=31.7 Hz), 112.91, 111.56, 71.03, 28.08, 10.29; DEPT spectrum: quaternary carbons δ 149.32, 146.19, 131.46, 125.33, 118.27; CH carbons δ 127.73, 126.8, 124.44, 119.88, 112.91, 111.56, 71.03; CH_2 carbon δ 28.08; CH_3 carbon δ 10.29; IR (drifts) 3292 (s), 3038 (m), 2975 (m), 1621 (s), 1331 (s), 1320 (s), 1114 (vs); Anal. Calcd for $C_{16}H_{15}N_4F_3$: C, 59.99; H, 4.72; N, 17.49. Found (first crop): C, 60.16; H, 4.74; N, 17.86. Found (second crop): C, 59.97; H, 4.66; N, 17.63.

Example 3

cis-(2-Ethyl-6-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl)-carbamic acid benzyl ester

A one liter, four neck flask under nitrogen atmosphere was charged with N-vinyl-carbamic acid benzyl ester (27.66 g, 156 mmol, 1.0 equiv) and dry toluene (500 mL). (1-Benzotriazol-1-yl-propyl)-(4-trifluoromethyl-phenyl)-amine (50.0 g, 156 mmol, 1.0 equiv) and *p*-toluenesulfonic acid monohydrate (297 mg, 1.56 mmol, 0.01 equiv) were added, and the mixture heated to 70°C. After 2 h, the mixture was cooled to room temperature and transfered to a separatory funnel. Ethyl acetate (500 mL) was added. The mixture was washed 1 x 200 mL 1N NaOH, 1 x 200 mL H_2O, 1 x 200 mL brine, and dried ($MgSO_4$). The mixture was filtered and the solids washed 1 x 50 mL ethyl acetate. The filtrate was concentrated to approximately 250 mL. 500 mL toluene were added, and the mixture concentrated to approximately 500 mL. 500 mL n-heptane were added, the slurry was stirred 1 h, filtered through a Buchner funnel, and dried. cis-(2-Ethyl-6-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl)-carbamic acid benzyl ester was isolated as a white powder (45.04 g, 76%): mp 155-157 °C; ^{1}H NMR (DMSO-d6, 400 MHz) δ 0.92 (t, 3H, J=7.5 Hz), 1.5 (m, 3H), 2.00 (m, 1H), 3.35 (m, 1H), 4.77 (m, 1H), 5.07 (d, 1H, J=12.5 Hz), 5.15 (d, 1H, J=12.5 Hz), 6.35 (s, 1H), 6.61 (d, 1H, J=8.5 Hz), 7.12 (s, 1H), 7.18 (dd, 1H, J=1.9, 8.5 Hz), 7.4 (m, 5H), 7.70 (d, 1H, J=9.1 Hz); ^{13}C NMR (DMSO-d6, 100 MHz) δ 157.03, 149.02, 137.79, 128.82, 128.23, 128.03, 125.9 (q, J=270 Hz), 125.06, 123.50, 121.73, 115.2 (q, J=31.7 Hz), 113.33, 65.85, 52.09, 47.83, 34.02, 28.68, 9.93; DEPT spectrum: quaternary carbons δ 157.03, 149.02, 137.79, 125.9, 121.73, 115.2; CH carbons δ 128.82,

128.23, 128.03, 125.06, 123.50, 113.33, 52.09, 47.83; CH_2 carbons δ 65.85, 34.02, 28.68; CH_3 carbon δ 9.93; IR (drifts) 3430 (m), 3303 (s), 2951 (m), 1686 (vs), 1542 (vs), 1088 (vs); MS (APCI+) m/z (rel. intensity) 379 ($M+H^+$, 53), 228 (100); Anal. Calcd for $C_{20}H_{21}N_2O_2F_3$: C, 63.48; H, 5.59; N, 7.40; Found: C, 63.69; H, 6.06, N, 7.36.

Example 4

cis-4-Benzyloxycarbonylamino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

A three liter, four neck flask under nitrogen atmosphere was charged with cis-(2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl)-carbamic acid benzyl ester (96.0 g, 254 mmol, 1.0 equiv), dry dichloromethane (720 mL), and dry pyridine (103 mL, 1.27 mol, 5.0 equiv). A solution of ethyl chloroformate (121 mL, 1.27 mol, 5.0 equiv), in dry dichloromethane (240 mL), was added slowly over 4 h. The addition was exothermic and required a reflux condenser. Once the chloroformate addition was complete, the reaction was cooled in an ice bath and 1350 mL 1N NaOH were added. The mixture was stirred 15 min, then transferred to a separatory funnel. The layers were separated and the aqueous extracted 1 x 1L dichloromethane. The combined dichloromethane layers were washed 1 x 1350 mL 1N HCl, 1 x 1L saturated aq. $NaHCO_3$, 1 x 1L brine, and dried (Na_2SO_4). The mixture was filtered, and the filtrate concentrated to an orange oil. 570 mL abs. ethanol were added, and the solution was concentrated. The solids were dissolved in 1370 mL abs. ethanol. 570 mL H_2O were added dropwise over 45 min. The resultant thick slurry was stirred 18 h and filtered. The solids were washed with cold 7:3 abs. ethanol/water (1 x 250 mL, then 1 x 100 mL) and dried (vac oven, 45°C) to give cis-4-benzyloxycarbonylamino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester as a white, crystalline solid (94.54 g, 83%): mp 92-96°C; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.84 (t, 3H, J=7.4 Hz), 1.28 (t, 3H, J=7.0 Hz), 1.4 (m, 2H), 1.62 (m, 1H), 2.53 (m, 1H), 4.23 (m, 2H), 4.47 (m, 1H), 4.79 (m, 1H), 5.01 (d, 1H, J=9.2 Hz), 5.18 (m, 2H), 7.4 (m, 5H), 7.5 (m, 2H), 7.57 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.97, 154.43, 139.44, 136.21, 134.33, 128.61, 128.33, 128.22, 126.32 (q, J=31.7 Hz), 126.18, 124.22, 124.19, 124.12 (q, J=273 Hz), 120.74, 120.70, 67.22, 62.24, 53.47, 46.79, 37.75, 28.25, 14.38, 9.78; DEPT spectrum: quaternary carbons δ 155.97, 154.43, 139.44, 136.21, 134.33, 126.32, 124.12; CH carbons δ 128.61,

128.33, 128.22, 126.18, 124.22, 124.19, 120.74, 120.70, 53.47, 46.79; CH_2 carbons δ 67.22, 62.24, 37.75, 28.25; CH_3 carbons δ 14.38, 9.78; IR (drifts) 3304 (s), 3067 (m), 3033 (m), 2982 (m), 2932 (m), 1723 (s), 1693 (s), 1545 (s); MS (APCI+) m/z (rel. intensity) 451 ($M+H^+$, 2), 300 (100); Anal. Calcd for $C_{23}H_{25}N_2O_4F_3$: C, 61.33; H, 5.60; N, 6.22. Found: C, 61.07; H, 5.69; N, 6.22.

Example 5

cis-4-Amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

A one liter, four neck flask under nitrogen atmosphere was charged with cis-4-benzyloxycarbonylamino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (40.1 g, 89 mmol, 1.0 equiv), methanol (400 mL), and ammonium formate (14.0 g, 223 mmol, 2.5 equiv). 10% Pd/C, 50% water wet (4.0 g) was added, and the slurry heated to 40° C over 1 h. After 1.5 h, the mixture was cooled to room temperature and filtered through Celite®. The cake was washed 2 x 100 mL methanol. The filtrate was concentrated to approximately 75 mL, transferred to a separatory funnel, and diluted with 400 mL ethyl acetate. The mixture was washed 1 x 125 mL saturated aq. $NaHCO_3$, 1 x 100 mL brine, and dried (Na_2SO_4). The mixture was filtered and the filtrate concentrated to a clear oil. The oil was crystallized from 100 mL n-heptane to give cis-4-amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester as a white crystalline solid (26.05 g, 93%): mp 61.5-63.5° C; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.79 (t, 3H, J=7.5 Hz), 1.24 (m, 4H), 1.42 (m, 1H), 1.51 (br s, 2H), 1.62 (m, 1H), 2.46 (m, 1H), 3.73 (m, 1H), 4.17 (m, 2H), 4.36 (m, 1H), 7.44 (m, 2H), 7.66 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.6, 139.3, 138.9, 126.3 (q, J=32 Hz), 125.7, 124.3 (q, J=271 Hz), 123.5, 119.8, 61.96, 54.16, 46.91, 41.50, 28.85, 14.38, 9.60; DEPT spectrum: quaternary carbons δ 154.6, 139.3, 138.9, 126.3, 124.3; CH carbons δ 125.7, 123.5, 119.8, 54.16, 46.91; CH_2 carbons δ 61.96, 41.50, 28.85; CH_3 carbons δ 14.38, 9.60; IR (drifts) 3350 (s), 3293 (m), 2972 (s), 1697 (vs); MS (ES+) m/z (rel. intensity) 358 ($M+H+CH_3CN^+$, 55), 317 ($M+H^+$, 7), 300 (100); Anal. Calcd for $C_{15}H_{19}N_2O_2F_3$: C, 56.96; H, 6.06; N, 8.86. Found: C, 56.86; H, 6.28; N, 8.82.

Example 6

(-) (2R, 4S)-4-Amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester hemi-(-)-dibenzoyl-L-tartrate salt

A one liter flask under nitrogen atmosphere was charged with cis-4-benzyloxycarbonylamino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (24.0 g, 75.9 mmol, 1.0 equiv) and (-) dibenzoyl-L-tartaric acid (anhydrous) (27.19 g, 75.9 mmol, 1.0 equiv). 300 mL of approximately 97% ethanol (prepared by adding 10.5 mL H_2O to 500 mL absolute ethanol, mixing, and measuring out 300 mL) was added. The mixture was stirred at room temperature for 18 h, then filtered. The solids were washed 1 x 48 mL approximately 97% ethanol, and dried to give (-) (2R, 4S)-4-amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester hemi-(-)-dibenzoyl-L-tartrate salt as a white crystalline solid (14.77 g, 39%): mp 189.5-191.5 °C (dec); ^{1}H NMR (DMSO-d6, 400 MHz) δ 0.62 (t, 3H, J=7.3 Hz), 1.16 (t, 3H, J=7.1Hz), 1.3 (m, 3H), 2.5 (m, 1H), 4.1 (m, 4H), 5.63 (s, 1H, methine proton in DBTA), 7.47 (m, 2H, DBTA aromatic H's), 7.6 (m, 3H, DBTA aromatic H's), 7.68 (s, 1H), 7.95 (m, 2H), 8.2 (br s, NH_3^+, did not integrate); ^{13}C NMR (DMSO-d6, 100 MHz) δ 169.85, 165.53, 154.10, 140.14, 134.59, 133.51, 130.74, 129.69, 128.98, 126.74, 124.82 (q, J=31.7 Hz), 124.69 (q, J=271 Hz), 124.50, 120.90, 74.49, 62.14, 53.51, 45.94, 38.81, 28.23, 14.63, 9.58; DEPT spectrum: quaternary carbons δ 169.85, 165.53, 154.10, 140.14, 134.59, 130.74, 124.82, 124.69; CH carbons δ 133.51, 129.69, 128.98, 126.74, 124.50, 120.90, 74.49, 53.51, 45.94; CH_2 carbons δ 62.14, 38.81, 28.23; CH_3 carbons δ 14.63, 9.58; IR (drifts) 3278 (m), 2400-3100 (broad), 1703 (vs); MS (ES+) m/z (rel: intensity) 358 ($M+H+CH_3CN^+$, 55), 317 ($M+H^+$, 7), 300 (100); Anal. Calcd for $C_{15}H_{19}N_2O_2F_3.C_9H_7O_4$: C, 58.18; H, 5.29; N, 5.65. Found: C, 57.99; H, 5.15; N, 5.64; Chiral HPLC: mobile phase 950:50:2 n-hexane:2-propanol:HOAc, flow rate 1.50 mL/min, column temp 40°C, chiralpak™ AD 4.6 x 250 mm, sample concentration approximately 0.5 mg/mL in approximately 1:1 n-hexane:2-propanol. Authentic racemate shows retention times of 7.5 min and 10.0 min. (-) (2R, 4S)-4-Amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester hemi-(-)-dibenzoyl-L-tartrate salt: 10.0 min, 88.9%, 7.5 min <<1%, 2.0 min (solvent front) 11.1%; $[\alpha]_D$ = -153 (c=1.07, CH_3OH).

Example 7

(-)-(2R, 4S)-4-(3,5-Bis-trifluoromethyl-benzylamino)-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester tosylate salt

(-) (2R, 4S)-4-Amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester hemi-(-)-dibenzoyl-L-tartrate salt (13.0 g, 26.2 mmol, 1.0 equiv) was

suspended in 1,2-dichloroethane (260 mL) in a 500 mL separatory funnel. The mixture was washed 1 x 65 mL 1N NaOH, 1 x 65 mL brine, and dried ($MgSO_4$). The mixture was filtered, concentrated to approximately approximately 80 mL, and transferred to a 250 mL three neck flask. 3,5-Bis(trifluoromethyl)benzaldehyde (4.53 mL, 27.5 mmol, 1.05 equiv) was added, and the mixture stirred 1 h at room temperature under nitrogen atmosphere. Sodium triacetoxyborohydride (11.1 g, 52.4 mmol, 2.0 equiv) was added in one portion, and the white slurry was stirred 18 h. 50 mL 1,2-dichloroethane and 50 mL 2N NaOH were added, and the aqueous layer extracted 2 x 50 mL 1,2-dichloroethane. The combined organic extracts were washed 1 x 31 mL 1N HCl, 1 x 50 mL saturated aq. $NaHCO_3$, 1 x 50 mL brine, and dried (Na_2SO_4). The mixture was filtered and concentrated to a clear oil. The oil was dissolved in methanol (71 mL). *p*-Toluenesulfonic acid monohydrate (5.23 g, 27.5 mmol, 1.05 equiv) was added. After 5 min, 284 mL isopropyl ether was added. The solution was concentrtated to approximately 35mL, transferred to a 500 mL three neck flask (mech. stirrer), and diluted with 284 mL isopropyl ether. A thick white slurry formed in 10 minutes. After stirring 3 h, the slurry was filtered and the cake washed 2 x 70 mL isopropyl ether. After drying, (-)-(2R, 4S)-4-(3,5-bis-trifluoromethyl-benzylamino)-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester tosylate salt was isolated as a white powder (16.18 g, 86% overall): mp 191-192°C; ^{1}H NMR (DMSO-d6, 400 MHz) δ 0.78 (t, 3H, J=7.5 Hz), 1.21 (t, 3H, J=7.0 Hz), 1.5 (m, 3H), 2.24 (s, 3H), 3.08 (m, 1H), 4.17 (m, 2H), 4.41 (m, 1H), 4.50 (m, 2H), 4.79 (m, 1H), 7.04 (d, 2H, J=7.9 Hz), 7.42 (d, 2H, J=7.9 Hz), 7.7 (m, 2H), 7.81 (s, 1H), 8.21 (s, 1H), 8.35 (s, 2H), 9.58 (br s, 1H), 9.83 (br s, 1H); ^{13}C NMR (DMSO-d6, 100 MHz) δ 154.00, 145.46, 140.21, 138.39, 135.33, 132.51, 131.62, 130.79 (q, J=33.2 Hz), 128.49, 127.40, 125.82, 125.36, 124.99 (q, J=31.7 Hz), 124.59 (q, J=271 Hz), 123.69 (q, J=273 Hz), 123.44, 120.33, 62.32, 53.99, 53.79, 47.98, 33.30, 28.61, 21.13, 14.63, 9.58; DEPT spectrum: quaternary carbons δ 154.00, 145.46, 140.21, 138.39, 135.33, 130.79, 124.99, 124.59, 123.69; CH carbons δ 132.51, 131.62, 128.49, 127.40, 125.82, 125.36, 123.44, 120.33, 53.99, 53.79; CH_2 carbons δ 62.32, 47.98, 33.30, 28.61; CH_3 carbons δ 21.13, 14.63, 9.58; IR (drifts) 2300-3100 (broad), 2974 (m), 2731 (m), 2620 (m), 2455 (m), 1714 (s), 1621 (m), 1283 (vs), 1169 (vs), 1126 (vs); MS (ES+) m/z (rel. intensity) 584 ($M+H+CH_3CN^+$, 100), 543 ($M+H^+$, 80); Anal. Calcd for $C_{24}H_{23}N_2O_2F_9.C_7H_8O_3S$: C, 52.11; H, 4.37; N,

3.92. Found: C, 52.15; H, 4.22; N, 3.69; $[\alpha]_D$ = -77.9 (c = 1.05, CH_3OH).

Example 8

(-)-(2R, 4S)-4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester mono ethanolate

Na_2CO_3 (s) (6.75 g, 63.7 mmol, 3.5 equiv) was added to a room temperature solution of (-)-(2R, 4S)-4-(3,5-bis-trifluoromethyl-benzylamino)-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester tosylate salt (13.0 g, 18.2 mmol, 1.0 equiv) in dry THF (130 mL). Methyl chloroformate (3.51 mL, 45.5 mmol, 2.5 equiv) was added neat, dropwise over 2 min. After 24 h, the mixture was concentrated to 65 mL, diluted with 260 mL ethyl acetate, and transferred to a separatory funnel. The mixture was washed 1 x 90 mL 1N HCl (CO_2 evolution), 1 x 90 mL saturated aq. $NaHCO_3$, 1 x 90 mL brine, and dried ($MgSO_4$). Filtration and concentration of filtrate afforded a clear oil, which was costripped 3 x 33 mL 2B ethanol. The oil was dissolved in 33 mL 2B ethanol and seeded with a few milligrams of (-)-(2R, 4S)-4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester mono ethanolate. After stirring 18 h at room temperature, the slurry was filtered and dried to give (-)-(2R, 4S)-4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester mono ethanolate as a white crystalline powder (8.66 g, 74%): mp 54-58 °C; ^1H NMR ($CDCl_3$, 400 MHz, 55°C) δ 0.73 (t, 3H, J=7.0 Hz), 1.20 (t, EtOH), 1.27 (t, 3H, J=7.1 Hz), 1.42 (m, 2H), 1.66 (m, 1H), 2.25 (br s, 1H), 3.67 (q, EtOH), 3.79 (s, 3H), 4.2 (m, 3H), 4.33 (m, 1H), 5.2 (br s, 2H), 7.12 (s, 1H), 7.49 (d, 1H, J=8.3 Hz), 7.57 (d, 1H, J=8.5 Hz), 7.73 (s, 2H), 7.78 (s, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 157.74, 154.37, 141.73, 140.05, 133.83, 132.14 (q, J=33 Hz), 126.94, 124.49, 123.96 (q, J=273 Hz), 123.13 (q, J=273 Hz), 121.31, 119.17, 62.29, 58.28, 54.42, 53.71, 53.08, 46.67, 37.01, 29.02, 18.29, 14.32, 9.22, (note: the fourth quartet appears to be buried under the δ 126.94 peak, with J approximately 32 Hz); DEPT spectrum: quaternary carbons δ 157.74, 154.37, 141.73, 140.05, 133.83, 132.14, 123.96, 123.13; CH carbons δ 126.94, 124.49, 121.31, 119.17, 54.42, 53.08; CH_2 carbons δ 62.29, 58.28, 46.67, 37.01, 29.02; CH_3 carbons δ 53.71, 18.29, 14.32, 9.22; IR (drifts) 3489 (s), 2974 (s), 2884 (m), 1701 (vs), 1280 (vs), 1131 (vs); MS (ES+) m/z (rel. intensity) 601 ($M+H^+$, 100); Anal. Calcd for $C_{26}H_{25}N_2O_4F_9.C_2H_6O$: C, 52.01; H, 4.83; N, 4.33. Found: C,

51.84; H, 4.54; N, 4.33; chiral HPLC: mobile phase 950:50:2 n-hexane:2-propanol:HOAc, flow rate 1.0 mL/min, 254 nm, chiralpak AD 4.6 x 250 mm, column temp 40°C, sample concentration approximately 0.5 mg/mL in 90:10 n-hexane:2-propanol, authentic racemate retention times 3.6 and 4.6 min. (-)-(2R, 4S)-4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester mono ethanolate shows 4.6 min, 99.1% and 3.6 min, not detected; $[\alpha]_D$ = -93.3 (c = 1.08, CH_3OH).

Example 9

Anhydrous, (-)-(2R,4S)-4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester.

A 2.6g portion of 4(S)-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2(R)-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (a mixture of predominantly amorphous material with traces of ethanolate crystalline form; the title compound was also prepared in an analogous manner starting from pure amorphous or pure ethanolate material) was charged to 13 milliliters of hexanes and heated to effect a solution at about 60°C. The heat was removed and the reaction was allowed to cool to ambient over a one hour period. The reaction was seeded with anhydrous (-)-(2R,4S)-4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester and granulated for eighteen hours under ambient conditions. Alternately, the anhydrous crystals may be prepared from hexanes without seeding. The product was collected by filtration and air dried. The isolated product X-ray pattern matched the calculated powder pattern.

Density: 1.406

Crystal System: Trigonal

Microscopy: Well formed rods and equant (fractured rods) crystals demonstrating high birefringence when viewed across the C axis. Being in the Trigonal crystal system the crystals do not demonstrate birefringence when viewed down the C axis. The crystals demonstrate a cleavage plane perpendicular to the C axis.

Fusion Microsocopy: In Type A oil--------dissolution at 50°C.

Dry----------clear melt at 86°C.

NMR: No trace of ethanolate

Degree of crystallinity: Highly crystalline

Hygroscopicity: Non-hygroscopic at 100% relative humidity over 48 hours.

Appearance: Free flowing white powder.

The X-Ray diffraction d-spacing is provided in Table 2.

TABLE 2

Anode: CU – Wavelength 1: 1.54056 Wavelength 2: 1.54439 (Rel Intensity: 0.500)
Range #1 – Coupled: 3.000 to 40.000 StepSize: 0.040 StepTime: 1.00
Smoothing Width: 0.300 Threshold: 1.0

d(A)	1(rel)	d(A)	I(rel)	d(A)	I(rel)
11.21659	34.8	5.52958	60.0	4.04469	36.6
10.50618	12.0	5.39152	75.7	3.89345	39.6
9.66890	11.0	5.24818	80.5	3.72038	80.7
8.88669	4.1	4.84992	13.2	3.64330	15.0
7.31083	3.7	4.44170	100.0	3.49463	5.9
6.34185	56.4	4.32558	16.8	3.44831	7.2
6.09484	5.9	4.25150	31.0	3.33631	14.7
5.92806	38.4	4.08413	42.7	3.22157	6.7

d(A)	I(rel)	d(A)	I(rel)
3.16983	8.3	2.57207	8.5
3.11970	14.0	2.49503	3.6
2.96985	16.3	2.44562	
2.87051	8.7	2.42250	
2.81002	6.8	2.38844	
2.75539	6.8	2.36135	
2.70226	3.6	2.32612	
2.64524	8.9		

Example 10

Monoethanolate, (-)-(2R,4S)-4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester.

4.0 grams of (-)-(2R,4S)-4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester were dissolved in 3.5 ml ethanol and sonicated for two minutes to complete dissolution. A white solid formed to which 10 ml ethanol was added and stirred at ambient temperature overnight. A white powder was filtered and collected on 0.22 μm LS filter paper followed by washing with about 15 ml. ethanol. The isolated product X-ray pattern matched the calculated powder pattern.

Density: 1.402

Crystal System: orthorhombic

Microscopy: crystalline needles with moderate birefringence.

Fusion Microsocopy: In Type A oil-----melt and dissolution at 43°C with loss of water

Dry----------clear melt at 43°C

NMR: shows ethanol of solvation

Degree of crystallinity: highly crystalline

Hygroscopicity: non-hygroscopic

Appearance: free-flowing white power

The X-Ray diffraction d-spacing is provided in Table 3.

TABLE 3

Anode: CU – Wavelength 1: 1.54056 Wavelength 2: 1.54439 (Rel Intensity: 0.500)
Range #1 – Coupled: 3.000 to 40.000 StepSize: 0.040 StepTime: 1.00
Smoothing Width: 0.300 Threshold: 1.0

d(A)	1(rel)	d(A)	I(rel)	d(A)	I(rel)
22.15759	37.6	5.69284	6.9	4.18443	23.3
8.61222	15.1	5.45839	5.8	4.03073	30.9
8.15185	9.5	5.19975	19.0	3.96396	33.9
7.83462	47.0	4.90695	53.6	3.83314	35.0
7.47295	100.0	4.68527	42.1	3.77447	40.8
7.00403	9.6	4.80453	18.9	3.72125	33.1
6.46476	17.2	4.38780	16.3	3.62106	26.6
6.23035	14.8	4.30354	19.7	3.52462	17.1
5.90921	7.9				

d(A)	I(rel)	d(A)	I(rel)
3.44170	12.6	2.77147	5.0
3.35282	6.7	2.70399	7.5
3.25110	11.7	2.63859	4.6
3.12884	5.7	2.53872	6.4
3.03164	4.4	2.49493	5.3
2.94892	5.8	2.47186	5.0
2.86853	4.2	2.34837	4.7
2.79318	4.3	2.26951	4.1

Example 11

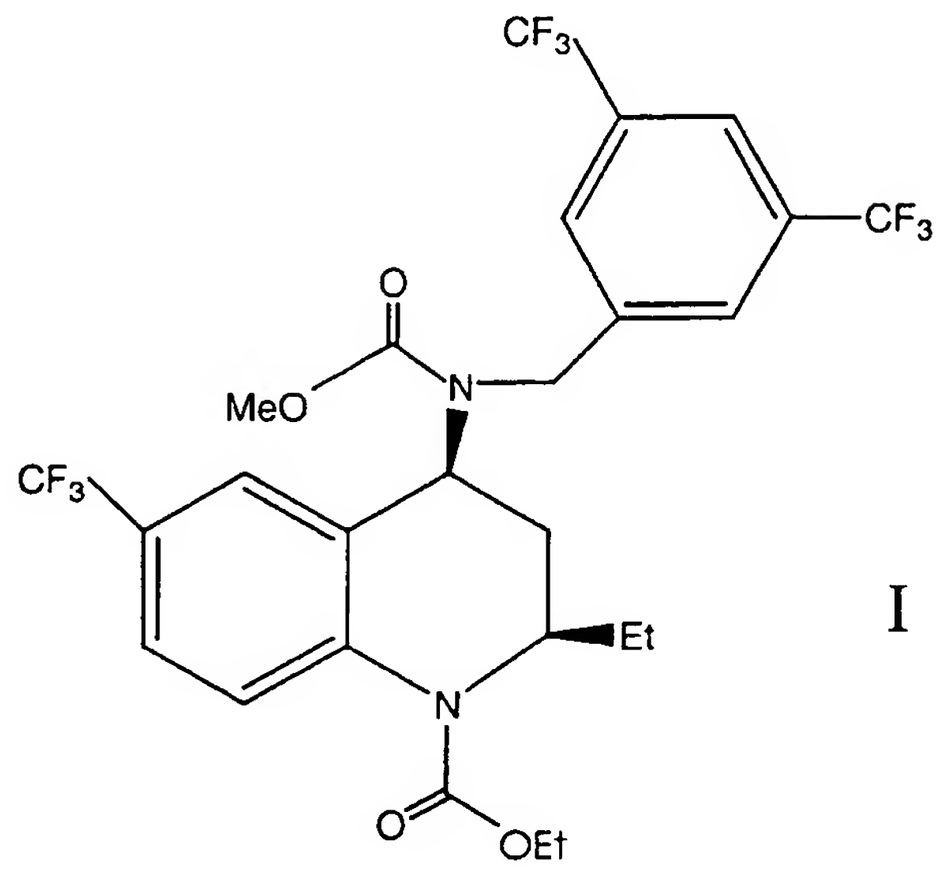
Anhydrous (-)-(2R,4S)-4-[(3,5-bis-trifluromethylbenzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester.

A crude solution of approximately 42 g of (-)-(2R,4S)-4-[(3,5-bis-trifluromethylbenzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester in 500 ml of ethyl acetate (obtained via the process described in Example 8) was concentrated under vacuum to a volume of 100-135 ml. The remaining ethyl acetate was displaced with 3 X 220 ml 2B EtOH to a final volume

of 100-135 ml. This solution was seeded with a crystal of anhydrous (-)-(2R,4S)-4-[(3,5-bis-trifluromethylbenzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester. After stirring 18 hr at room temperature the slurry was filtered and vacuum dried to give 19.81 g of anhydrous (-)-(2R,4S)-4-[(3,5-bis-trifluromethylbenzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester. The melting point behaviour was the same as the material prepared via Example 9 confirming the anhydrous nature of the material.

CLAIMS

1. A crystalline form of the compound of formula I



I

2. A crystal which is anhydrous [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester.

3. A crystal which is the ethanolate of [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester.

4. A crystal of claim 1 which is the anhydrous crystal having the x-ray powder diffraction d-spacing

Anode: CU – Wavelength 1: 1.54056 Wavelength 2: 1.54439 (Rel Intensity: 0.500)
Range #1 – Coupled: 3.000 to 40.000 StepSize: 0.040 StepTime: 1.00
Smoothing Width: 0.300 Threshold: 1.0

d(A)	1(rel)	d(A)	I(rel)	d(A)	I(rel)
11.21659	34.8	5.52958	60.0	4.04469	36.6
10.50618	12.0	5.39152	75.7	3.89345	39.6
9.66890	11.0	5.24818	80.5	3.72038	80.7
8.88669	4.1	4.84992	13.2	3.64330	15.0
7.31083	3.7	4.44170	100.0	3.49463	5.9
6.34185	56.4	4.32558	16.8	3.44831	7.2
6.09484	5.9	4.25150	31.0	3.33631	14.7
5.92806	38.4	4.08413	42.7	3.22157	6.7

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d(A)	I(rel)	d(A)	I(rel)
3.16983	8.3	2.57207	8.5
3.11970	14.0	2.49503	3.6
2.96985	16.3	2.44562	
2.87051	8.7	2.42250	
2.81002	6.8	2.38844	
2.75539	6.8	2.36135	
2.70226	3.6	2.32612	
2.64524	8.9		

5. A crystal of claim 1 which is the ethanolate crystal having the x-ray powder diffraction d-spacing

Anode: CU – Wavelength 1: 1.54056 Wavelength 2: 1.54439 (Rel Intensity: 0.500)
Range #1 – Coupled: 3.000 to 40.000 StepSize: 0.040 StepTime: 1.00
Smoothing Width: 0.300 Threshold: 1.0

d(A)	1(rel)	d(A)	I(rel)	d(A)	I(rel)
22.15759	37.6	5.69284	6.9	4.18443	23.3
8.61222	15.1	5.45839	5.8	4.03073	30.9
8.15185	9.5	5.19975	19.0	3.96396	33.9
7.83462	47.0	4.90695	53.6	3.83314	35.0
7.47295	100.0	4.68527	42.1	3.77447	40.8
7.00403	9.6	4.80453	18.9	3.72125	33.1
6.46476	17.2	4.38780	16.3	3.62106	26.6
6.23035	14.8	4.30354	19.7	3.52462	17.1
5.90921	7.9				

d(A)	I(rel)	d(A)	I(rel)
3.44170	12.6	2.77147	5.0
3.35282	6.7	2.70399	7.5
3.25110	11.7	2.63859	4.6
3.12884	5.7	2.53872	6.4
3.03164	4.4	2.49493	5.3
2.94892	5.8	2.47186	5.0
2.86853	4.2	2.34837	4.7
2.79318	4.3	2.26951	4.1

6. A pharmaceutical composition which comprises a therapeutically effective amount of a crystal of claim 1 and a pharmaceutically acceptable carrier, vehicle or diluent.

7. The pharmaceutical composition as recited in claim 6 wherein the pharmaceutical composition comprises an atherosclerosis, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia, cardiovascular disorders, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, vascular

complications of diabetes, obesity or endotoxemia treating amount of the crystal of claim 1 and a pharmaceutically acceptable carrier, vehicle or diluent.

8. The pharmaceutical composition as recited in claim 6 for the treatment of atherosclerosis which comprises an atherosclerosis treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

9. The pharmaceutical composition as recited in claim 8 wherein the atherosclerosis treating amount of the Formula I crystal is about 0.1 to 10 mg/kg/day, and the pharmaceutical composition was prepared by dissolving the crystal of claim 1 in a fatty oil.

10. The pharmaceutical composition as recited in claim 8 wherein the Formula I crystal is anhydrous.

11. The pharmaceutical composition as recited in claim 8 wherein the Formula I crystal is the ethanolate crystal.

12. A method of inhibiting CETP in a mammal in need thereof which comprises the administration of a CETP inhibiting amount of the Formula I crystal as recited in claim 1.

13. The method as recited in claim 12 comprising treating atherosclerosis, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia, cardiovascular disorders, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, vascular complications of diabetes, obesity or endotoxemia by administering to a mammal, in need of such treatment a therapeutically effective amount of the Formula I crystal.

14. The method as recited in claim 13 wherein atherosclerosis is treated with an atherosclerosis treating amount of the Formula I crystal.

15. The method as recited in claim 14 wherein the atherosclerosis treating amount of the Formula I crystal is about 0.1 to 10 mg/kg/day and the Formula I crystal was dissolved in a fatty oil.

16. The method as recited in claim 15 wherein the Formula I crystal is anhydrous.

17. The method as recited in claim 15 wherein the Formula I salt is the ethanolate.

18. A process for preparing crystalline anhydrous [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-

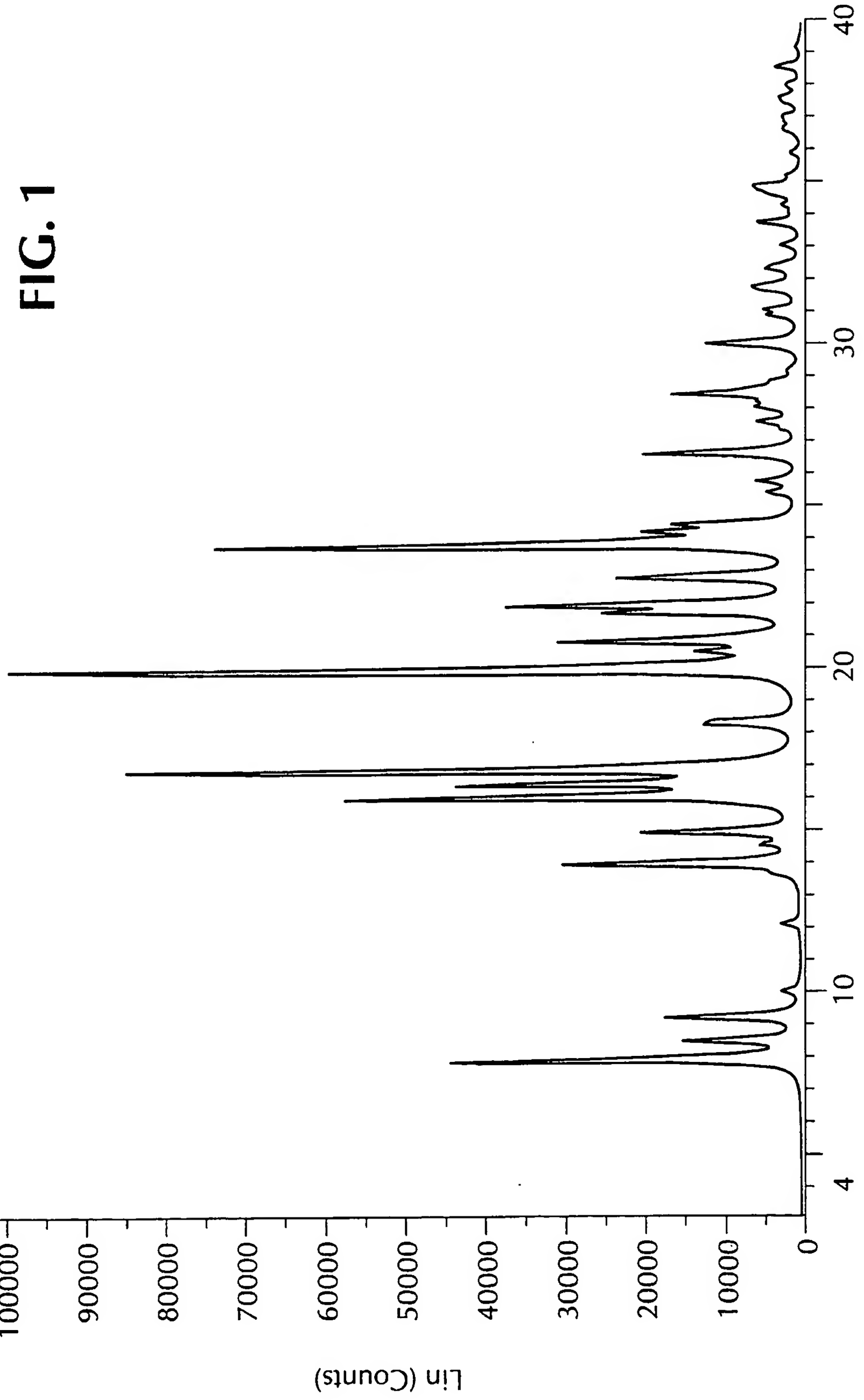
2H-quinoline-1-carboxylic acid ethyl ester comprising dissolving or mixing [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester in hexanes at ambient temperature for about 2 to about 24 hours wherein said precursor is not an anhydrous crystalline form.

19. A process for preparing crystalline ethanolate [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester by dissolving or mixing [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester in ethanol/water at ambient temperature for about 0.5 to about 18 hours wherein said precursor is not a crystalline ethanolate form.

20. The process as recited in claim 19 wherein ethanol is used without water.

21. A process for preparing crystalline anhydrous [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester comprising dissolving or mixing [2R,4S] 4-[3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester in ethanol at ambient temperature for about 2 to about 24 hours wherein said precursor is not an anhydrous crystalline form.

FIG. 1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70000
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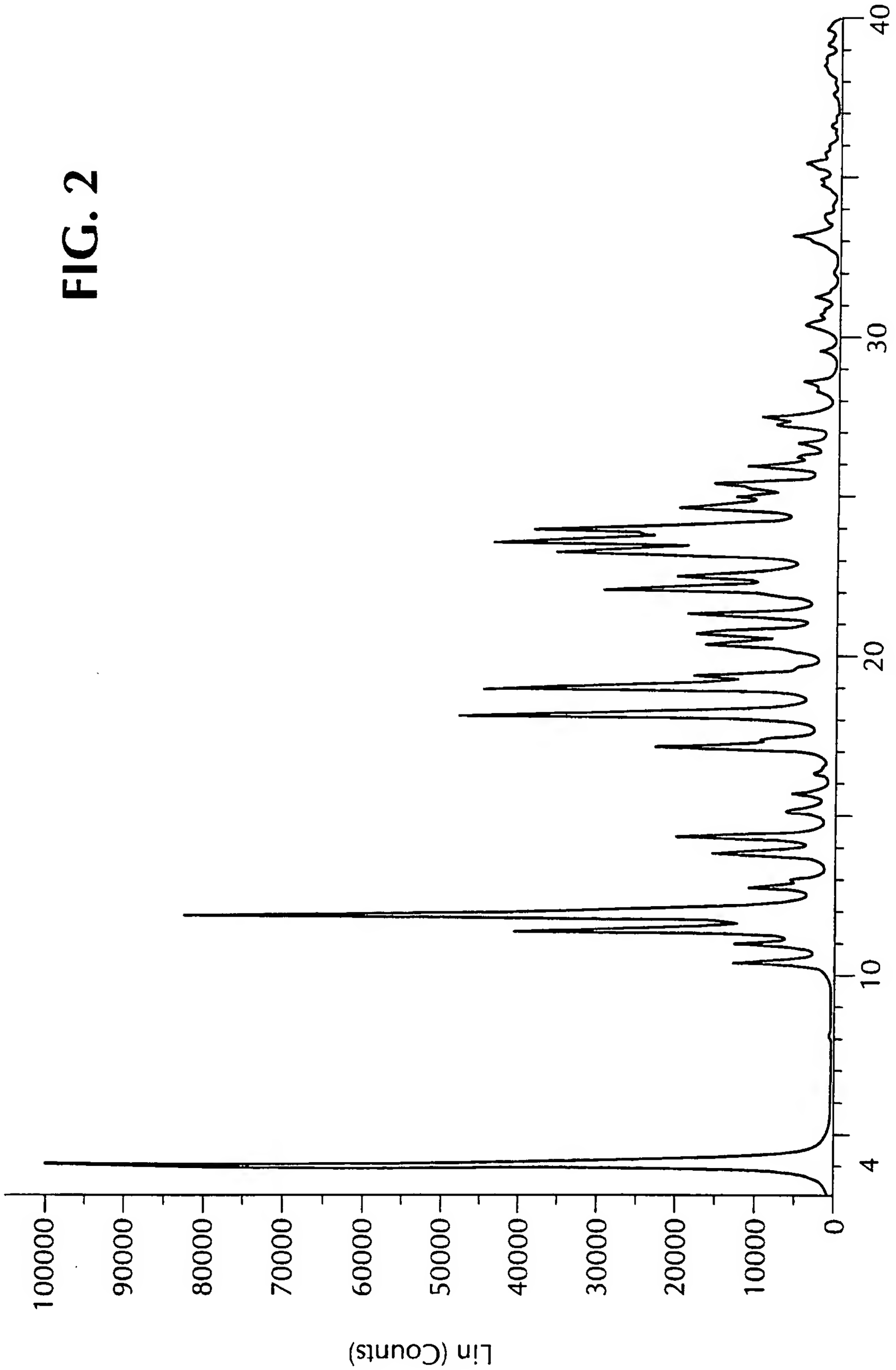
50000
40000
30000
20000
10000
0
4
10
20
30
40
2-Theta - Scale

FIG. 2


Lin (Counts)
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
4
10
20
30
40
2-Theta - Scale

INTERNATIONAL SEARCH REPORT

Interr. nal Application No
PCT/IB 00/01650

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D215/42 A61K31/47 A61P9/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 00 17164 A (WESTER RONALD THURE ;PFIZER PROD INC (US); DENINNO MICHAEL PAUL (U) 30 March 2000 (2000-03-30) page 66, line 14-16; example 120	1-11, 18-21
A	WO 98 33775 A (AMERICAN HOME PROD) 6 August 1998 (1998-08-06) page 1; claim 1	1-11
A	US 5 231 102 A (BAKER RAYMOND ET AL) 27 July 1993 (1993-07-27) column 1-2	1-11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 January 2001	23/01/01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Lauro, P

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 00/01650

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 12 to 17 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/IB 00/01650

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		NO 901082 A	10-09-1990
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